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SCIENTIFIC RESEARCH ON THE HEALTH OF VIETNAM VETERANS

HEARING

BEFORE THE

SUBCOMMITTEE ON
HOSPITALS AND HEALTH CARE

OF THE

COMMITTEE ON VETERANS' AFFAIRS
HOUSE OF REPRESENTATIVES

ONE HUNDREDTH CONGRESS

SECOND SESSION

JUNE 8, 1988

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SCIENTIFIC RESEARCH ON THE HEALTH OF VIETNAM VETERANS

WEDNESDAY, JUNE 8, 1988

U.S. House of Representatives,
Committee on Veterans' Affairs,
Subcommittee on Hospitals and Health Care,
Washington, D.C.

The subcommittee met, pursuant to notice, at 9 a.m., in room 334, Cannon House Office Building, Hon. J. Roy Rowland of Georgia (acting chairman of the subcommittee) presiding.

Present: Representatives Montgomery, Penny, Rowland of Georgia, Stenholm, Kennedy, Hammerschmidt, McEwen, Ridge, and Solomon (ex officio).

Also present: Representative Evans.

Dr. **Rowland of Georgia** (acting chairman). The hearing will come to order, please.

Good morning. Chairman Montgomery is not going to be able to be here initially this morning, so I want to read his statement.

Opening Statement of Hon. G. V. (Sonny) Montgomery, Chairman, Full Committee on Veterans' Affairs

The purpose of our hearing this morning is to receive testimony on the status, findings, and interpretations of scientific research related to the health of Vietnam veterans, including health related to exposure to Agent Orange. This is an oversight hearing; proposed legislation regarding compensation will not be addressed this morning.

This is the fourteenth hearing we have held on the relationship between Vietnam service, including exposure to Agent Orange, and the health of Vietnam veterans. Such emphasis is entirely appropriate because of concerns that were raised in the late 1970's about possible adverse health effects arising from veterans' exposure to Agent Orange in Vietnam. It is also appropriate because of the emotion and controversy that surround these topics.

What gets lost sometimes in talking about the health of Vietnam veterans is that we all hope that there will prove to be no risk of disease or disability and no systematic threat from previous exposures or experiences in Vietnam. Today, we hope to provide a clearer picture of the overall state of the science and research on which we depend as we grapple with this complex, divisive, emotional, and vitally important issue.

We have been and continue to be committed to the most comprehensive scientific analysis that is possible. Many witnesses who are with us today represent a number of scientific entities which have conducted or reviewed research related to the health of Vietnam veterans. The efforts and resources that have been expended are impressive. These efforts have even resulted in the development of a new scientific method of testing blood for the presence of dioxin.

This new method furnishes a way to establish exposure to dioxin about which so much controversy has occurred. Discriminating between exposure and nonexposure has been a major barrier to studying the link between Agent Orange and health.

The fact remains, however, that the long-term health effects of Agent Orange exposure in Vietnam pose questions of science that have stretched the capacity of researchers to answer. On that basis, some people question the way that their nation has treated Vietnam veterans.

In this regard, it is useful to recount Congressional actions accomplished legislatively for Vietnam veterans, that is:

Provided eligibility for VA health care for Vietnam veterans who believe their illness is due to exposure to Agent Orange in Public Laws 97-72 and 99-166. Public Law 99-272 made this a requirement.

Required the VA to conduct an epidemiological study of Vietnam veterans to evaluate health effects of exposure to Agent Orange and to review the literature on health effects of exposure in Public Law 96-151. Public Law 97-72 expanded the study to include health effects from the experience in Vietnam.

Required VA, through public rulemaking, to develop policies and procedures for the adjudication of veterans' claims for compensation and other benefits based on their exposure to Agent Orange in Public Law 98-542.

Established Vet Centers to provide readjustment counseling to Vietnam veterans in Public Law 96-22.

Today, we hope to receive testimony that will demonstrate the distance we have come with regard to understanding the relationship between health and service in Vietnam.

I especially want to thank the witnesses today. Many, if not all of them, have been involved in this topic since the beginning. Their steadfast work deserves the thanks of all of us.

Dr. **ROWLAND OF GEORGIA**. At this point, I want to make a comment about some scientists in CDC who have worked so hard in this project overall, trying to assess the problems that we are trying to address here today. As I understand it, there are five scientists there who have spent a great deal of time, and I want to express appreciation for what they have done there.

Now, I want to recognize my good friend, John Paul Hammerschmidt of Arkansas, the ranking member of this subcommittee, for any remarks that he may wish to make.

OPENING STATEMENT OF HON. JOHN PAUL HAMMERSCHMIDT

Mr. **HAMMERSCHMIDT**. Thank you very much, Mr. Chairman.

First, may I congratulate the chairman, Sonny Montgomery, for scheduling this hearing to give us an update on various studies with respect to Agent Orange and respect to related matters.

Dr. Rowland, in Sonny's absence, it is very appropriate that you be chairing this committee, because I know of your long-time great interest in this particular matter before us. It is a very emotional issue with many veterans. They strongly believe that certain disabilities that they may have are related to exposure to Agent Orange. They believe, too, that various deformities or disabilities of their children also result from exposure.

Mr. Chairman, in my view, these beliefs, as of now, I emphasize, are simply not supported by scientific fact. This committee has been a strong supporter of the many studies that have taken place or which are on-going in this area. Millions and millions of dollars have been spent to try to obtain the facts. Many more will be spent in the future.

This is because we want to do the responsible thing with respect to benefits and services for the veterans involved.

Mr. Chairman, as you know, veterans who were exposed to Agent Orange and who have disabilities that may have been associated with that exposure, are entitled now to priority medical care from the Veterans' Administration. They can also receive examinations and have their names and the results of the examination entered on a register for possible future consideration for compensation if future scientific findings so indicate.

Mr. Chairman, we ought not to pre-judge science. We ought not to consider this extremely important matter on emotion.

For my part, I want to see the final results of the studies that are the subject of our hearings today. Our witnesses represent the great scientific community of our nation. I am certain that their testimony will be based on compassionate understanding that the issue before them is one that requires the very best efforts possible.

As the facts continue to unfold, Mr. Chairman, I am also certain that, under your leadership, this committee will make informed judgments as to what legislative course of action ought to be taken. That judgment will be in the great tradition of this committee. It will presume a disability relationship with exposure to Agent Orange if the facts so indicate. It will resolve reasonable doubt in favor of veterans, again, if the facts so indicate.

In short, Mr. Chairman, this committee will lead the Congress in doing the right and responsible thing.

Mr. Chairman, I might mention that I have full committee hearings over in Public Works and Transportation that are beginning at 9:30. So, when I depart, it is not from lack of interest in this hearing by any means, but I thought I would explain to our witnesses and the other members of the committee about that other conflict.

Thank you, Mr. Chairman.

Dr. **ROWLAND OF GEORGIA**. Thank you, Mr. Hammerschmidt. I am aware of those hearings, too, since I also serve on that Public Works Committee, and I know there will be a great deal of activity there today.

I would like to recognize now my colleague, Lane Evans.

OPENING STATEMENT OF HON. LANE EVANS

Mr. **EVANS**. Thank you, Mr. Chairman. I want to thank you and Sonny Montgomery for calling this important hearing to review Agent Orange studies.

I am interested in learning what progress has been made with regard to these studies. As you know, over 11 million gallons of Agent Orange were sprayed over 6,000 square miles of Vietnam to destroy the enemy's jungles. For years it has been suspected that this deadly chemical has severely damaged the health of hundreds of thousands of soldiers who served there.

Many have ailments, including cancer, and their children are suffering from birth defects. For these veterans and their families, the effects of Agent Orange have become a daily struggle that harms their lives and futures.

Despite Congressional prodding and calls for action, the Government's efforts to determine the health hazards of Agent Orange exposure has, in my opinion, been a woeful tale of foot-dragging and inaction. In September, it was learned that the Veterans' Administration failed for more than six months to properly disclose the results of a study that found that Vietnam veterans are more likely than those that served elsewhere to die from illnesses that have been associated with Agent Orange exposure.

The Government's conduct, in my opinion, has been unconscionable. For too long, it has failed to fulfill its obligations to those who served this nation in good faith. Neither the Federal Government nor our nation's veterans can afford another eight years and the $63 million it took to look into this question. Thousands of Vietnam veterans suffering from Agent Orange exposure need help now. There is no reason for further delay.

So, again, thank you. I appreciate your allowing me to sit in on this hearing. I am not a member of this subcommittee, and I look forward to the witnesses before us today.

Thank you very much.

Dr. ROWLAND OF GEORGIA. Thank you, Lane.

As I am sure many people know, Lane and I came to the Congress at the same time, and I don't know of anyone who has gotten out front and worked more aggressively to try to address the problems of Vietnam veterans than Lane Evans. He has really been outspoken and has gotten me involved to a large extent because of his feelings about it.

Without objection, Senator John Kerry has asked that his statement be placed in the record, and that will be done.

[The statement of Senator Kerry appears on p. 67.]

Dr. ROWLAND OF GEORGIA. Now I would like to recognize my good friend from New York, Jerry Solomon, the ranking member of the full committee.

OPENING STATEMENT OF HON. GERALD B.H. SOLOMON

Mr. SOLOMON. Thank you, Mr. Chairman.

I won't take but a minute. As you know, we have been in a meeting that you were at previously with Sonny Montgomery. I don't think he is far behind, but I want to commend Chairman Montgomery and our ranking member, John Paul Hammerschmidt, for holding these oversight hearings.

I do apologize—I have a Foreign Affairs meeting going on right now that I have to get to, but I will try to get back before this hearing is over.

Thank you very much.

Dr. ROWLAND OF GEORGIA. Thank you very much, Mr. Solomon.

My friend from Massachusetts, Joe Kennedy.

OPENING STATEMENT OF HON. JOSEPH P. KENNEDY, II

Mr. KENNEDY. Thank you very much, Mr. Chairman.

Distinguished members of the committee, ladies and gentlemen, I find it disturbing that many Federal agencies have not been more responsive in addressing our veterans' concerns about Agent Orange. The VA was mandated by Congress to conduct a study in 1979 investigating the possible adverse health effects related to the exposure to Agent Orange for our nation's Vietnam veterans.

Four years later, the VA, against a backdrop of their own admission of skepticism of the veterans' claims, had no report for the Congress, and the responsibility for this study was transferred to the Centers for Disease Control in 1983. $63 million later, the CDC aborted their study in 1987, blaming difficulty identifying an appropriate study population using veterans' medical records.

It is extremely unfortunate that the agency which is alleged to be at the forefront of epidemiological research could not come up with an alternative study design.

Mr. Chairman, our nation's veterans are growing impatient. $91 million has been spent thus far on dioxin-related research and an additional $122 million for ongoing projects. An estimated $188 million more is required to complete these ongoing projects, and we are still at square one.

Scientists bicker back and forth, each one invalidating the other's study. Meanwhile, our veterans who have served in one of our nation's toughest wars wait for our Government to decide whether or not they will receive compensation for certain illnesses.

In the interim, while Congress waits for these studies to produce scientific facts, I hope we would include certain cancers such as non-Hodgkin's lymphoma to be included in compensation for service-related disabilities. Our veterans are not asking for handouts or windfalls. All they ask is to be able to be compensated for the medical attention that they deserve.

Thank you, Mr. Chairman.

Dr. **Rowland of Georgia**. I thank my good friend from Massachusetts who has also been very much involved in trying to look out for the Vietnam veterans' interests.

If there are no other statements from members, I want to call the first witness to the talbe, the Honorable Thomas Harvey, the Deputy Administrator for Veterans' Affairs at the Veterans' Administration.

Mr. Harvey, thank you very much for being here this morning. Please proceed in your own manner, if you will.

STATEMENT OF HON. THOMAS HARVEY, DEPUTY ADMINISTRATOR OF VETERANS' AFFAIRS, VETERANS' ADMINISTRATION; ACCOMPANIED BY L. B. HOBSON, DIRECTOR, AGENT ORANGE PROJECT OFFICE

Mr. **Harvey**. Good morning, Mr. Chairman, and thank you very much for providing me with the opportunity to appear before the subcommittee this morning.

Mr. Chairman, if I may, I would like to just have my formal remarks placed in the record in full, and I would like to summarize those briefly.

Dr. **Rowland of Georgia**. Without objection.

Mr. **Harvey**. Mr. Chairman, there is no more difficult issue that we are dealing with today, I think, in the Veterans' Administration than the subject of Agent Orange. Agent Orange has taken on many of the aspects of symbolism of the entire Vietnam experience.

With that, you have elements of anger, of guilt, of guilt from those who didn't serve in Vietnam who possibly left the country or sought to take advantage of various types of student deferments that were available to them at the time, guilt of Vietnam-era veterans who themselves may have availed themselves of ways to avoid actual service in-country but who served during that period not in Vietnam, and guilt of Vietnam theater veterans who, if you were to speak to them candidly, would admit to you that indeed their Vietnam service was not all that they would have you believe.

The fact is, only some 20 percent of those who served in Vietnam served with combat units, infantry, artillery, and armor. The vast majority of those who served in-country served as support troops. As everyone knows, the tooth to tail ratio in Vietnam was something like 1 to 8 or 1 to 10, and that is probably being generous.

So, for many Vietnam veterans, actually, they really didn't see the combat that they would have someone believe as they dealt with them today.

It is also an issue that is fraught with fear. The Vietnam veteran is now, on average, 41 years old. The Vietnam veteran is on the upward slope of a bell curve of mortality. He has health problems commensurate with health problems expected of any other 41-year-old American male today. This may manifest itself in a number of different ways.

In addition, it is an issue that is filled with confusion.

It is an issue that has been studied for years. Indeed, the information that has been generated by science over these many years is information that should be considered to be good news to the Vietnam veteran. No significant epidemiological increases in disease have been noted in all the scientifically credible studies that have been done.

From our original concern that Agent Orange may be a time bomb ticking away in the Vietnam veteran, what we have seen is that Agent Orange, at least in the amounts most of the American veterans were exposed to, seems to cause no health problems in man or in his offspring.

Mr. Chairman, let me just take a minute, if I may, to talk about my own background. After law school and admission to the bar, I went on active duty as an infantry officer in 1966. I volunteered for airborne training. I was a senior parachutist. I was a ranger. I served in Vietnam for two and a half years.

If I may, Mr. Chairman, let me just show you. Mr. Chairman, this is a map of the Republic of Vietnam, and here we have—I have asked my staff to mark on here where Agent Orange was used in Vietnam.

I personally served one year in this area, the area around Ankhe, as a company commander with the 173rd Airborne Brigade. I also served a year and a half in this area up north of Tay Ninh City along the Cambodian border where I was an advisor with the Vietnamese airborne division.

In November of 1969, I received a Silver Star for action that occurred at this location where I was at a fire base that was very nearly overrun by North Vietnamese soldiers. In joint operations with the 1st of the 22nd mechanized division, down in this area generally, I received a Purple Heart in August of 1969.

I care about the issue of Agent Orange, Mr. Chairman, and I think that I have a very special reason to care. I was there. I served in these areas, and should it be determined scientifically that there are problems that are associated with exposure to Vietnam, I would very much like to know that, because those problems could very much affect me.

At a hearing on this same subject before the Senate Veterans' Affairs Committee a few weeks ago, one of the witnesses was upset because I had had an opportunity to speak about my own Vietnam experience, and he did not have that opportunity. Mr. Chairman, I would like to suggest that in the future when veterans do approach you and say they are Vietnam veterans and would like to address these issues of concern to them, invite them to do just that. Invite them to speak about their Vietnam experience. Invite them to tell you where they served, what unit they served with, when they were there, and what their military occupational specialty was.

Let me tell you a little bit about some of the people at the Veterans' Administration who deal with issues like this, Mr. Chairman. Right up here is the area where Fred Downs whom many of you know lost his left arm in Vietnam. Fred is the head of the Prosthetic Service at the Veterans' Administration.

Jim Mayer lost both of his legs in this area up in the Hobo Woods/Iron Triangle area. Jeft Duvall, another friend of mine and colleague, took an AK47 round through the femur in action in this location. Bill Clouden served out in this area in the delta, and he was injured and medivac'd from Vietnam. Bob Klear, another colleague of mine, served with the 11th Army Cavalry Regiment in this area as an 18-year-old sergeant in the Army.

Mr. Chairman, these people make up the Veterans' Administration, and they are people who have concerns for America's veterans and for all of the issues that affect them. Their concern is based on a lifetime of commitment professionally, following their military service in the Republic of Vietnam.

One thing I might also suggest, Mr. Chairman, when you are approached by veterans who speak of concerns like this and who introduce themselves as disabled veterans—you might also want to consider asking them just what is their disability, what degree of compensation are they receiving from the Veterans' Administration, and how that disability was incurred.

Mr. Chairman, I can understand how a veteran would be concerned about these issues. I can understand the pain that a veteran who has a handicapped child feels as he looks at that child that he loves every single day he wakes up and says I love this kid and I wonder what happened to him. Could it possibly be something that I did, that I am responsible for?

One of the allegations that is consistently made about the Veterans' Administration with regard to Agent Orange is that the Veterans' Administration is simply doing nothing. Mr. Chairman, that is just plain wrong.

The Veterans' Administration is providing health care to veterans. We have provided some 30,000 episodes of in-patient care to veterans who came to us saying that they had a physical problem they themselves believed was caused by exposure to Agent Orange. We have provided about 1.1 million episodes of out-patient care to veterans who have sought that sort of treatment.

In addition to that, over the years since 1981, we have provided an extensive literature review. I have here, Mr. Chairman, most of the volumes of this literature review. The 11th and 12th are still in publication and will be available soon.

This is an analysis of all the world's literature on Agent Orange, dioxin, and related matters, and it is really an important compendium of most of what we know about that. We have also published monographs on the subject of Agent Orange. We have published lay language summaries of this material.

Mr. Chairman, we have done a great deal in this area. We have attempted to share this information with anyone whom we can find who has an interest in it.

We have also conducted research. We have funded almost $100 million worth of research through the Centers for Disease Control. We do all this in a highly professional way, and our activities are subject to review by the Congressionally mandated Advisory Committee on Environmental Hazards that is made up of truly eminent *scientists who have* a professional competence in this area that, frankly, I don't bring to it.

What we are not doing is paying monetary compensation to veterans for problems that they believe were caused by Agent Orange. And we are not doing so because it simply hasn't been established by science that that causal relationship exists.

Now, let me just mention that about two weeks ago, we received a copy of a letter dated May 20 from the Centers for Disease Control to, I believe, the chairman and ranking minority members of both the House and the Senate committees making reference to the fact that some eight cases of non-Hodgkin's lymphoma had been discovered among Vietnam-era veterans that were studied and indicating that there is fertile ground there for further study.

I don't know what the significance of that particular letter is and, indeed, the letter itself says don't over-interpret this data. More study must be done.

I would prefer to do that and to see that study reviewed by our advisory committee before we express any thoughts on just what the conclusions are of that.

Mr. Chairman, there has been an attempt legislatively to respond politically to an issue such as this that calls for scientific answers. I oppose that legislation. I oppose that approach very strongly. I believe it is bad politics as well as bad science.

It is bad politics because it keeps the myth alive of Agent Orange as a cause of large problems among Vietnam veterans. It is bad politics because those who believe that this sop to Vietnam veterans will quiet the outcry with regard to this issue are surely going to be very seriously disappointed. If you don't have the scientific connection, causal relationship between the physical problem and the cause of exposure to Agent Orange, there just simply is no basis for providing monetary compensation.

It is bad politics because I believe that that sort of an approach to the issue of Agent Orange compensation calls into question the credibility of the entire Veterans' Administration disability compensation scheme, and I believe the American taxpayers are entitled to something better than that. I believe they are entitled to causative relationship being established first.

Finally, it is bad politics because it further perpetuates the myth of the Vietnam veteran as victim, and, Mr. Chairman, that is just not so.

It is bad science because the evidence simply isn't there.

Mr. Chairman, thank you for the opportunity to appear before the subcommittee this morning. It is a great pleasure to be here with you.

[The prepared statement of Mr. Harvey appears on p. 75.]

Mr. MONTGOMERY. Thank you very much, Tom Harvey, for your very strong testimony this morning.

Dr. Rowland?

Dr. ROWLAND OF GEORGIA. Thank you, Mr. Chairman.

Thank you, Mr. Harvey. I have two or three questions I want to ask you.

On page 1 of your opening statement, you said that the Agent Orange registry still does not show any unusual health patterns among the Vietnam veterans. What analyses or studies of the registry have led you to this conclusion?

Mr. HARVEY. Let me ask Dr. Hobson of the Veterans' Administration if he could just answer that from the floor.

Dr. HOBSON. The registry was not set up as a means for conducting a scientific investigation. It was a system for recording the people who felt that they had been injured by Agent Orange or might have been injured.

As such, it is a self-selected population, and we review the registry in an informal fashion, that is, a non-scientific fashion to see whether there are any patterns that emerge of unusual numbers or clusters of different kinds of cases. That has been done several times, the last time about two years ago. Never have we seen anything that indicated a cluster that could be attributed, possibly, to the experience in Vietnam, whether it was Agent Orange or something else.

Dr. ROWLAND OF GEORGIA. Not any malignancies or—

Dr. HOBSON. There are malignancies in it, but they are not of any particular type nor of any particular incidence.

Dr. ROWLAND OF GEORGIA. What about chloracne?

Dr. HOBSON. Chloracne we did not see in those examinations.

Dr. ROWLAND OF GEORGIA. So, there is no physical differences among those veterans that you were able to determine from the study of that registry?

Dr. HOBSON. No. We would expect much the same thing from any population of men of approximately the same age.

Dr. ROWLAND OF GEORGIA. Let me ask you another question. The write-up of the VA's proportionate mortality study of Army and Marine Corps veterans of the Vietnam War led many people to assume it was an Agent Orange study. In fact, as you noted in your statement, it can say nothing about Agent Orange or any other potential etiologic factor.

When do you anticipate completion of the five-year follow-up studies to the proportionate mortality study?

Dr. HOBSON. They will be finished at different times during the next year and a half approximately.

Dr. ROWLAND OF GEORGIA. So, by the end of 1980?

Dr. HOBSON. We would anticipate having completed those studies by the end of 1990.

Dr. ROWLAND OF GEORGIA. You mentioned in your statement, Mr. Harvey, the VA's literature review on herbicides that is currently being updated. I understand that both animal and human studies are included in the review.

Are there any trends in the findings in animal or human studies that would be of interest for today's hearing?

Mr. **HARVEY**. I don't think of anything, Dr. Rowland, except for the most recent studies released by the Centers for Disease Control published in the May 13 issue of the Journal of the American Medical Association and then this letter that I mentioned to you dated May 20 which mentions the eight cases of non-Hodgkin's lymphoma and indicates the need for some further follow-up on that, and we will do that follow-up.

Dr. **ROWLAND OF GEORGIA**. That was the only one that was mentioned in JAMA?

Mr. **HARVEY**. The JAMA article covered three different aspects. It covered psychological, physical, and genetic aspects of Vietnam veterans who served in Vietnam. Basically, it indicated that there were not significant physical differences, there were no significantly greater numbers of birth defects among veterans who served there, and with some exceptions that have to do with a slightly elevated amount of PTSD and alcoholism and drug abuse among Vietnam veterans, in general, there was not a significant difference between those who served and those who did not. In terms of the physical things, the lower sperm count was the principal thing that was indicated.

Dr. **ROWLAND OF GEORGIA**. CDC will testify for us this morning, and I am sure they will address that.

One other question. You reported that lay language synopses have been prepared on the first ten volumes of the VA's literature review on herbicides. Is there any attempt to weave the scientific literature together in a lay language summary, or do the individual synopses stand alone?

Mr. **HARVEY**. I think those individual synopses would stand alone on that body of scientific information that will be continually updated. The scientific literature is continually reviewed by our Advisory Committee on Environmental Hazards which is made up by statute of 11 eminent scientists and 4 lay individuals from the public sector who are men of truly impressive credentials.

Dr. **ROWLAND OF GEORGIA**. Thank you very much, Mr. Harvey.

Thank you, Mr. Chairman.

Mr. **HARVEY**. Thank you, Dr. Rowland.

Mr. **MONTGOMERY**. Thank you, Dr. Rowland.

The Chair will use the list as the way the members came in. Lane Evans?

Mr. **EVANS**. Thank you, Mr. Chairman.

Mr. Harvey, you know I respect your service experience. It is quite a distinguished record, but I just wondered if you are not denigrating the experiences of some other of our fellow veterans who have fought and defended this country. I don't know what your comments about mid-life crises were directed at, but would you attribute the problems that Admiral Zumwalt and his son are facing as documented in their book, "My Father; My Son" to some mid-life crisis that—

Mr. HARVEY. Not at all, Mr. Evans. Admiral Zumwalt's son has two different types of cancer. He also has a child who has a severe birth defect, and I am not sure what the nature of that is.

Admiral Zumwalt was a very fine Chief of Naval Operations. The fact is, however, he is not a scientist, and the scientific connection between the difficulties of his son and his grandson and exposure to Agent Orange in Vietnam simply hasn't been proven to exist.

Mr. EVANS. The VA's own mortality study that you just talked about does who a 58 percent higher cancer rate, I believe, and a 110 percent higher non-Hodgkin's lymphoma rate among I Corps veterans of the United States Marine Corps. It does not scientifically link those cancers, those higher rates of illness to Agent Orange or other herbicide exposure, but it indicates a much higher rate than, I guess, if I recall correctly, other Marine Corps veterans who did not serve in the I Corps area of Vietnam.

Simply to come before this committee and talk about rear echelon personnel and mid-life crises, I think, ignores the fact that we have those kinds of higher diseases for some reason, and we better find out why we have those kinds of illnesses. What factors are associated with that?

Our problems with the VA and the Centers for Disease Control have been that we have not had any kind of concrete study or real efforts on the part of the Administration to find out what these problems are. So, if you have 58 percent higher cancer rates and 110 percent higher non-Hodgkin's lymphoma rates, they are there for some reason. We simply can't ignore these people and write them off and all the claims of Vietnam veterans because it is Agent Orange. If it is not Agent Orange, I think we better find out what it is.

As far as rear echelon personnel, I was told in the very first year that I was in Congress at a briefing held by the Veterans' Administration that the military was so negligent in the disposal of 55-gallon barrel drums in which these herbicides were sent to Vietnam that the Vietnamese quite often, being as resourceful as they were, would take the drums and use them for Moped fuel containers and that some of the residue mixed with that Moped and was even probably used in Mopeds in downtown Saigon.

So, even the most rear end echelon person in the American Red Cross could conceivably have been exposed to Agent Orange in downtown Saigon as an office PO working in some headquarters. So, I think we even have to worry about the rear end personnel.

I just don't think that, given the fact that not a single Vietnam veteran has ever been compensated, that we have good faith on the part of the Administration. I think we are here to decide what the politics of Agent Orange are going to be.

We have tried to be a non-partisan committee as much as possible, but I find it regrettable that you are coming up here and telling us what the politics of this ought to be. We will decide that. That is what we are elected to do, and we are going to continue to explore this issue—I hope not only from a political point of view but a policy point of view.

While I respect your experience, I just think you are denigrating the service of so many other people who now have legitimate problems. Whatever they are, however they are caused, I think we need to get to the bottom of it very quickly, because we have just had a bill signed by President Reagan that after 40 years has finally given the atomic veterans of this country the compensation I think they should have gotten years ago.

I am pleased that this country has finally lived up to that obligation. I just don't want to see it be 40 years before we live up to our obligation to the Vietnam veterans that are having problems.

Mr. **Harvey**. I am pleased to have an opportunity to answer your question.

Mr. Evans, first of all, you mentioned mortality rate among veterans encountered in the proportionate mortality study, and that was quite a study. It covered 50,000 people, and we did a tremendous amount of work on that.

What it indicated was that there was an incidence of mortality that is somewhat higher from two diseases among Marines who served in I Corps, non-Hodgkin's lymphoma and lung cancer. It was not a rate. It was a specific incidence of those particular problems, and that is significant in terms of the scientific evaluation of just what that study indicates for us and for those who are in a position to assess this matter scientifically.

In addition to that, we have been doing a great deal of work. You are ascribing to us sort of a failure to act. What we are not doing is coming up with the answers that a number of Vietnam veterans would like to hear, but we have done a lot of scientific study.

We are looking for causative relationships from exposure to Agent Orange or from other substances. The CDC recently released a study published in the Journal of the American Medical Association that covered a broad range of different things, and these things have been studied in a lot of different places.

Now, if we do come up with a causative relationship with anything that may be incidental to either service in Vietnam or service otherwise in the military, we compensate those. We are compensating about 3 million people right now for disabilities incurred in or aggravated by their military service.

Finally, you mentioned that we are not compensating anyone for anything relating to Vietnam, and that is obviously—

Mr. **Evans**. I didn't say that. I said in regard to Agent Orange compensation, and I just wonder how objective you are when you come before this committee and say the "myth of Agent Orange" or words to that effect causing problems among a large number of Vietnam veterans.

If you are in charge of looking over these studies and you think it is a myth, isn't that showing a lack of objectivity on your part when you are already dismissing the claims of at least a large number of Vietnam veterans as being myths?

Mr. **Harvey**. I don't do that myself, of course. We have our adjudicators who do that—

Mr. **Evans**. You said it was bad politics, did you not?

Mr. **Harvey**. I did say it was bad politics, but that is a little different than the myth, although I think that the two—perpetuating a myth with regard to Vietnam service, I think, is bad politics and really unfair to those of us who served in Vietnam.

Mr. **Montgomery**. The time of the gentleman has expired. The Chair would be glad to go around and come back to the gentleman.

Joe Kennedy.

Mr. KENNEDY. Thank you, Mr. Chairman.

Mr. Harvey, you know, there have been people in my family that have served in the Armed Forces who have records that they, I am sure, are proud of. I have never once heard any of them describe in the kind of detail that you described for us this morning their combat experiences, and what that has to do with this hearing this morning is beyond me.

For you to come into this hearing room and talk about the upward slope of the bell curve of mortality sounds like a page out of Ron Ziegler's book. To talk about this problem as a mid-life crisis, to refer to Vietnam veterans as having problems with kids on drugs as if they are some sort of segment of our population that has a particular problem in this regard, to indicate that only 20 percent of the people who served in Vietnam actually saw combat duty—I don't know what in God's name these supposed facts have to do with the purpose of the hearing this morning other than to make you look good.

I am outraged by your attitude of putting yourself forward here as an individual that we are somehow supposed to look up to because of your war record and putting that on the line to try to confuse this committee as to what the heck is going on with this study or the lack of a study or the inaccuracies of this study is something that, if I were you, I would be ashamed of.

I want to put that in the record and make certain that people who aren't in this committee understand how I feel about what you said this morning.

Mr. HARVEY. Do I have an opportunity to respond to that, Mr. Kennedy, or do you want to ask a question, too?

Mr. KENNEDY. You will in a second.

My question, sir, has to do with my opening statement. Back in 1979, an initial study was done that tried to relate health effects to exposure to Agent Orange with our nation's Vietnam veterans. Four years later, the VA, against a backdrop of their own admission of the skepticism of the veterans' claims, had no report for the Congress.

$63 million was later spent on the aborted CDC study. $122 million has been spent in addition with another additional $188 million more required to complete another study.

At some point, doesn't it just stand out with the basic human instincts that the United States went into the war in Vietnam to try to espouse and expand on that this nation is a nation that cares about people, that if we can't come up with direct causal links between a particular disease and the agents that were directly responsible or maybe indirectly responsible, don't you think that if the body of scientific knowledge suggest that if in fact you are exposed that there is a reasonable likelihood that these kinds of diseases will come forward?

In fact, the whole purpose of the Veteran's Administration is to look out for our veterans. Don't you think that our Veterans' Administration should be trying to look out for the veterans rather than trying to get out of a commitment to paying their health care bills?

These aren't people who are asking for millions of dollars worth of benefits. They are asking for specific benefits that they feel are a direct result of their involvement in that war.

It seems to me that they ought to be given an opportunity to have their health paid for.

Mr. HARVEY. Mr. Kennedy, we do that. We provide health care to Vietnam veterans who have problems that they themselves identify as being related to exposure to Agent Orange.

You mentioned the Veterans' Administration. The reason I mentioned a half a dozen of the guys that I work with who served in Vietnam, who were injured in Vietnam, who lost limbs in Vietnam, and who have since then devoted their professional lives to a career in the Veterans' Administration is to show we have people who care. Our agency is committed to doing that.

Now, the results may not be the results that somebody wants to hear, but we are trying, and we are spending the money, and we are investing the resources, and we simply have not come up with a scientific connection between exposure to a particular substance or other aspects of the Vietnam experience and particular illnesses.

Should that be done or should Congress direct us to do this and appropriate the money to do that, we will provide those monetary benefits. But we are providing health care right now. We are investing in the scientific basis that would be, I would hope, an essential underpinning of the ultimate decision to do something for veterans.

Mr. EVANS. Would the gentleman yield?

Mr. KENNEDY. Yes.

Mr. EVANS. You say that you are treating them for illnesses that they link to exposure to Agent Orange.

Mr. HARVEY. Yes.

Mr. EVANS. Do you link those illnesses to exposure to Agent Orange?

Mr. HARVEY. No, we do not.

Mr. EVANS. So, this is a matter of these veterans saying it is a problem with Agent Orange exposure, not an admission by the VA that these are Agent Orange related illnesses.

Mr. HARVEY. No. Congress directed that we provide that care as a Category A priority just as we provide care for service-connected disabled, prisoners of war, radiation survivors.

Mr. EVANS. Not in a single case have you ever treated somebody, by your own admission, by the VA's admission, that that is an illness linked to herbicide exposure because of a person's experience in Southeast Asia.

Mr. HARVEY. That is correct.

Mr. EVANS. Thank you.

Mr. KENNEDY. My time is up, Mr. Chairman.

Mr. MONTGOMERY. Let the Chair say this. This is an emotional issue, and when we say things here today, it is from emotion. The witness is handling himself well. The questioners are hitting at the heart of the situation. So, we understand it. You have to do this in building records.

I know, Tom, that your father is here and your sister is here, and we want to welcome them to the committee and the other people who are in the audience here today.

As I said, it is an emotional issue, and we have to do what we think is necessary from the witness stand and from Members of Congress.

Tom Ridge?

Mr. RIDGE. Thank you, Mr. Chairman.

Mr. Harvey, it is a pleasure to be in your company today, and I, for one, know a little bit about your service and applaud that two and a half years you spent over there and thank you for testifying.

Mr. HARVEY. Thank you, sir.

Mr. RIDGE. Although I would tell you I do have some concerns and reservations about the issue and the approach that has been undertaken, not just by this Administration but by a series of Administrations, and I would like to just ask you some questions about that.

First of all, one of the problems, I guess, that we have had in the past is defining those men or women that were exposed to a significant degree to Agent Orange. Hasn't that been a problem with all our studies in trying to design a protocol?

Mr. HARVEY. Yes, it has.

Mr. RIDGE. I am not trying to excuse it, because I happen to think there might be some ways around it, but I know when you made reference to the 3 million men and women who served and about 20 percent served in combat, I believe you were referring to the fact that the defoliant was most often used in areas of extreme vegetation where only those with military occupational specialties were likely to tread. Is that right?

Mr. HARVEY. Well, Mr. Ridge, on the map here—and I am sorry, because I think you probably can't get a very good look at this—we have indicated on the map with an orange colored overlay where Agent Orange was primarily used, and, indeed, yes, a lot of it was used in exactly those areas and also to defoliate perhaps around fire bases where others may serve.

Mr. RIDGE. I don't know too much about Agent Orange in Moped gas tanks, but last time I heard, you didn't spray downtown Saigon, did you? Just out of curiosity?

Mr. HARVEY. That is true.

Mr. RIDGE. I didn't think you did.

Let me ask you this from a scientific point of view. Has the VA examined the presence or absence of scientifically sanctioned tests to establish dioxin levels in either blood or tissue and/or scientifically acceptable tests that would distinguish between the chemical characteristics of the Agent Orange dioxin and other dioxins to which individuals, veterans or non-veterans, could be exposed? Is there an ongoing effort to work with the scientific community to identify tests or means to assess exposure, extent of exposure, and type of exposure?

Mr. HARVEY. Yes, there is, and a lot of that is reflected in the blue volumes I have here on the table with me. Volumes 11 and 12 of this review of the scientific literature that is being generated around the world are currently in production and will be printed and, again, circulated to everyone who has expressed an interest in this subject matter.

We are doing that and the more significant of these studies are evaluated by the Congressionally mandated Advisory Committee on

Environmental Hazards, and I believe we are probably the single most significant repository of information about dioxin anywhere simply because we have been directed by Congress to pursue this subject matter, and we have done so, I believe, responsibly and with alacrity.

Mr. **Ridge**. One of the concerns I have, I guess, is that if we look to establish with an absolute degree of medical or scientific certainty the nexus between exposure to Agent Orange and the variety of maladies that may result from that exposure, we may indeed wait 40 or 50 years in spite of the efforts of the VA, in spite of the efforts of other countries, in spite of all the tests we run.

I guess I have often wondered whether or not the VA has undertaken an effort with the National Academy of Sciences or other scientific and medical organizations throughout the world to determine whether or not there is a substantial and credible body of medical opinion that would say yes, based on what we know, based upon exposure to Agent Orange, these particular, we can say, not with an absolute degree of scientific certainty, but we can say with a reasonable degree of scientific or medical certainty that we can conclude that exposure to Agent Orange resulted in these problems. Is that—

Mr. **Harvey**. Yes, we have done that. We have done that. We continue to do that.

The fact is that we don't come up with any indication that there is any—not even a preponderance of the evidence—any even slight indication that particular problems may be caused by this.

Now, in our proportionate mortality study where we did discover the higher incidence of lung cancer and non-Hodgkin's lymphoma among Marines serving in I Corps that triggered additional studies to try to determine if there is a causative relationship. Frankly, you and I both know—what do you get lung cancer from? You get it from smoking.

Now, one of the things we tried to determine was were the Marines who died of lung cancer heavy smokers, and we were not able to make that determination.

But the non-Hodgkin's lymphoma is going to be looked at further and analyzed further. The CDC has indicated that they had eight cases from their own study, and they will be pursuing this in attempting to determine if there is causative relationship or even an indicia that there may be a problem here.

The fact is we are not looking for absolute certainty as we address this issue. The Veterans' Administration has a compensation scheme that weighs very heavily for the benefit of the veteran. Any reasonable doubt is resolved in favor of the veteran. In fact, many of the presumptive illnesses that we have on a list of some 41 presumptive illnesses—I think there would be serious question about whether or not many of those—age onset, diabetes, multiple sclerosis—were tied to veterans' service many years prior to the time that those are incurred.

As I said, we have a system that is very favorably disposed toward the veteran. We have a system where no one is rewarded for denying benefits to a veteran.

I can tell you from the two years I have been at the VA, I work with an awful lot of people who really are committed to that concept that veterans are something very special, that they served their country in a time of need, whatever their duty was, be it in combat as mine was or be it as a cook back in the base camp. They did that, and because they did that, we will administer the programs authorized by Congress and for which we are funded really with compassion and concern and dedication to those people.

Mr. RIDGE. If I might, I have just one follow-up question, Mr. Chairman.

Calling on your—

Mr. MONTGOMERY. Mr. Stenholm?

Mr. RIDGE. Well, I will wait until Mr. Stenholm has finished.

Mr. MONTGOMERY. Okay. Charlie?

Mr. STENHOLM. Thank you, Mr. Chairman.

Mr. Harvey, did I understand you to say that any Vietnam veteran who has a health problem that he or she may attribute to Agent Orange is receiving health care benefits?

Mr. HARVEY. They are receiving health care from the Veterans' Administration if they come to us and ask for that. Specifically, we have had 30,000 episodes of in-patient care. There would be some of those being the same people coming back multiple times. And we have 1.1 million episodes of out-patient care where we have provided care to individuals on that basis.

Mr. STENHOLM. Is it a fair statement—that any connection, whether real or imagined, qualifies for care? It is considered just like a service-connected disability with medical care given to that veteran?

Mr. HARVEY. And medical care is provided at the same priority as if that were a service-connected disability.

Now, if the fellow is hit by a truck outside the Veteran's Administration hospital and comes in with bones protruding from the fabric of his trousers, we may say this is not an Agent Orange issue. This is a traumatic injury. But in general—and it is because of Congressional mandate—I believe it was Public Law 99-72 directing us to provide that type of care.

Mr. STENHOLM. Mr. Chairman, I have been real interested in this entire testimony, the entire subject of Agent Orange. It coincides with my work on the other committee I serve on, the Agriculture Committee, and the whole question of chemicals, whether it be dioxin, whether it be something else. We have this same basic issue.

The very nature of chemicals and what they do—kill living organisms—is a very emotional subject. But I would hope that all parties would recognize the importance of establishing a cause and effect before we move further than we have already done, recognizing that in fact we have had studies not only in the United States but in other countries which are concerned about their veterans and have also attempted to find a cause and effect.

Mr. HARVEY. Yes, extensive studies in Australia, New Zealand, and following a chemical accident in Seveso in northern Italy. Yes, sir.

Mr. STENHOLM. And have any of those studies differed from those studies that we have conducted as a result of the concern of this committee and other committees of the Congress about whether or not Agent Orange causes the things that some believe it does?

Mr. HARVEY. No. The studies have been generally consistent with what we have generated scientifically in this country.

Mr. STENHOLM. And we have studies ongoing today and will continue to look for cause and effect involving this chemical and other chemicals.

My point is that I would like to depend upon scientific fact rather than emotion, whether it be this chemical or any other, because we are a nation that depends on chemicals for our very ability to survive.

My major point is that we have studies going on and we will continue to look. And the moment we find a cause and effect, I would have reason to believe that this committee would lead the charge in doing what is absolutely right and necessary.

Mr. HARVEY. And, Mr. Stenholm, if we should come up with that indication, I can tell you we will be up here in no time at all to let you know of the problems. We simply haven't found it, and we are, as you say, committed to pursuing a scientific answer to a scientific problem that calls for that type of an answer, not the political answer of simply providing monetary compensation.

Health care is already there, but not the political answer of simply providing monetary compensation for a particular group unless we can come up with a causal relationship between exposure to Agent Orange and the particular problem that somebody is speaking to us about, and we are pursuing that, but it just isn't there now.

Mr. STENHOLM. Thank you.

Mr. MONTGOMERY. Thank you very much, Charlie. You can be very helpful on this in that, as you said, you have been dealing in chemicals yourself for a number of years being in farming and also working on that committee.

Let the Chair say that I have always said that if we have problems with Agent Orange and it is causing Americans who fought over there to come down with disease, especially cancer, we want to take care of it, but we have to have some evidence. We have to have something to put our teeth in and figure out how we go about it.

Gosh, we must have had millions of dollars worth of studies, and we continue to do that.

Tim Penny?

Mr. PENNY. I have no questions, Mr. Chairman.

Mr. MONTGOMERY. Okay. Tom?

Mr. RIDGE. Mr. Chairman, I do have quite a few questions to follow up, and I would ask unanimous consent that I be able to submit them in writing so you can proceed. I know you have a long list of witnesses, and I don't mean to hold you up.

Mr. MONTGOMERY. I know the Chair is maybe taking a little longer on this, but the Veterans' Administration is really the key witness here today, so the Chair doesn't have any problems if you want five more minutes.

Mr. RIDGE. Fine, I would like that.

Mr. MONTGOMERY. Go ahead.

Mr. RIDGE. Mr. Harvey, some of the men and women in various veterans' advocacy groups feel strongly that there is a cause and effect, a nexus, between Agent Orange and non-Hodgkin's lymphoma. Several of them are advocating a presumption of disability based on what they believe is a reasonable degree of medical certainty and a credible body of medical information.

I would like to know if the VA has ever examined the sources employed by these people whom I respect and deal with all the time to see—just to examine that medical testimony to see what drives them to conclude that there ought to be a presumptive disability with regard to non-Hodgkin's lymphoma.

Mr. HARVEY. In general, those people are relying on the VA's own proportionate mortality study which indicated that there was a higher incidence of mortality from two diseases among a particular group of veterans who served in a particular place in Vietnam. One of those diseases was non-Hodgkin's lymphoma.

The study did not indicate and was not designed to seek out a causative relationship. What the study did was point to a problem and indicate that here are further avenues that must be pursued.

So, that was our own study that most of them are relying on.

Now, as I mentioned, on the 20th of May, CDC sent a letter to the chairmen and ranking minority members of both committees indicating something else that may point us in the direction of non-Hodgkin's lymphoma and a potential problem, but in their own letter they said this is only eight cases in total that they are looking at, and they said don't make the mistake of over-interpreting this data. What this does is indicate a direction we should continue to look.

And we will continue to look, and we look forward to the further refinement of the data from the Centers for Disease Control, but there certainly is nothing today that I think would support legislation that would provide for a presumption of service-connection for non-Hodgkin's lymphoma.

Meanwhile, however, we do provide health care for a veteran who comes in with a disease like that.

Mr. RIDGE. If a veteran comes in and complains of a rash or a kidney problem or something, you can substantiate his experience in Vietnam, and regardless of his MOS, are you telling me that you will treat that particular problem?

Mr. HARVEY. Yes, sir, I am. We will treat that.

Mr. RIDGE. Regardless of the nexus? Regardless of the cause and effect?

Mr. HARVEY. We don't pursue that at all. There is no problem with the health care. It really is just the monetary compensation, the disability compensation, money—where the problem exists.

Mr. RIDGE. Has the VA, the Center for Disease Control, or any of the other agencies been involved in the myriad of studies that have been conducted over the past several years examined any other environmental factors that could be involved in the skewing of some of these statistics? I mean, the focus has always been on Agent Orange, but it was a hostile environment in a lot of different ways.

I have often wondered whether or not there may be other environmentally related answers out there somewhere, or is the focus just strictly on cause and effect of Agent Orange?

Mr. HARVEY. One of the things that the proportionate mortality study said is, as it pointed towards possible other areas to pursue, is one of the things you might want to consider is was the anti-malaria medication that we took over there a possible cause, dapsone—

Mr. RIDGE. That is if you took it.

Mr. HARVEY. I took it. Dapsone, the little white pill, and chloroquine/primaquine, the big orange pill that you took once a week. Yes, we are pursuing other things such as that.

The fact is, however, that, in general, there are not skewed statistics. Even when you look at the proportionate mortality study, the absolute number of Marines in I Corps who died from, I believe, lung cancer, the expected mortality would have been 17 and there were 35. It is not big numbers that we are looking at, and the other studies have not indicated any spikes of a particular illness among this particular group.

I think that is one of the reasons that it is all the more important to look for the scientific connection, because if you were to say today to us to service-connect Non-Hodgkin's lymphoma in spite of the fact that the scientific relationship has not been established, why pick that one disease? Why not pick tooth decay? Why not pick any of the range of other diseases that anybody may suffer from.

The fact is—and I am sorry that Mr. Kennedy didn't care for the phrase—the average life expectancy of an American today is about 74 years. The average age of the Vietnam veteran is about 41. If you chart that curve of life expectancy, we are sort of at an age when people are beginning to die off. We are dying off from a range of different things, everything from automobile accidents to drug overdoses to heart attacks to various types of systemic cancers and we are doing it in the same proportion as other people in society of our age and background.

Mr. RIDGE. Finally, if I might, Mr. Chairman, a final comment. I know for years that the VA and the CDC tried to design a satisfactory scientific protocol that made them happy with the veterans population and content with some knowledge that these men were exposed to a particular—I think a minimum of 30 days to Agent Orange, and they were never able to put that protocol together.

I think, rightly so, the VA hopefully has shifted from trying to put together the scientific protocol to at least trying to find just simply out there in the body of medical information provided not only in this country but in the world just the cause and effects, as my colleague from Texas stated, just a cause and effect between exposure to Agent Orange regardless of whether for a day or for 30 days—and we may have to get to that when we deal with presumptions—but a nexus between exposure to Agent Orange and the diseases and the disabilities that may or may not be forthcoming.

I would just encourage you because of your legal background and your obvious interest in Vietnam veterans as well as the issue that trying to find the cause and effect to a degree of absolute certainty is not going to be done in the lifetime, I don't think, of Vietnam veterans, and I don't think we can wait nor should we wait.

So, I hope the focus is reduced a little bit to the extent that if there is a credible body of medical and scientific testimony and evidence that says there is a—it is very much like an expert witness in a civil lawsuit. Can you say with a reasonable degree of medical certainty that such an ailment or disease was caused by exposure to Agent Orange?

That is the approach that I hope the VA takes, because I just don't think we are going to find an absolute certainty, and I don't think the Vietnam veterans ought to wait for that scientific certainty to develop.

But I appreciate your testimony as well as your service.

Mr. HARVEY. I completely agree with you, Mr. Ridge, and that is exactly what we are looking for. I can tell you that my colleagues in the Veterans' Administration consistently throughout the agency are committed to that same sort of an approach.

Mr. RIDGE. Thank you.

Mr. HARVEY. Thank you.

Mr. MONTGOMERY. Without objection, Mr. Ridge and other members may submit questions, and we would appreciate it very much, Mr. Harvey, if these answers would come back from the Veterans' Administration.

Let me also say, Tom, we invite you to help us in this situation. You have been over and talked to me. You are a combat wounded veteran in Vietnam, and I want to point out to our witnesses today that he is on crutches, but that is not from Vietnam. That is from kicking a soccer ball or some sporting event.

However, Tom, we do need you here. We need your logical help in trying to come up with answers in this situation.

Thank you very much for being an excellent witness, Tom Harvey. Doctor, thank you for being here.

Mr. HARVEY. Thank you, Mr. Chairman.

Mr. MONTGOMERY. We have a panel on the next group. If you will come forward as I call your names, I appreciate your patience. It just takes time, and the Veterans' Administration is totally involved in this.

The Honorable Don Newman is Chairman, Domestic Policy Council, Agent Orange Working Group. Dr. Ronald Hart is Chairman of the Science Panel of the Agent Orange Working Group. Dr. James O Mason is Director of the Centers for Disease Control, and Dr. Vernon Houk is Director of the Center for Environmental Health and Injury Control.

As I understand it, Mr. Newman, you have something else that is very pressing. We understand that you want to make your statement and move out of the chair early. We certainly appreciate all the witnesses being here today.

Mr. NEWMAN. Thank you, Mr. Chairman.

I have lost the opportunity to join the Secretary at the meeting, so I have just sent word to him that I am engaged here with Chairman Montgomery. I think that will smooth the surface.

Mr. MONTGOMERY. It depends on which Secretary it is how much influence I might have.

[Laughter.]

Mr. NEWMAN. Secretary Bowen.

Mr. MONTGOMERY. Okay.

STATEMENT OF HON. DON M. NEWMAN, CHAIRMAN, DOMESTIC POLICY COUNCIL, AGENT ORANGE WORKING GROUP; ACCOMPANIED BY DR. RONALD HART, CHAIRMAN, SCIENCE PANEL, AGENT ORANGE WORKING GROUP

Mr. NEWMAN. As you have indicated, Mr. Chairman, my name is Don Newman. I am the Chairman of the Domestic Policy Council Agent Orange Working Group.

As you know, since 1979, the working group has served a coordinating role within the Government. In addition to facilitating discussions among Federal agencies and departments regarding the Agent Orange research direction, it has assured scientific peer review of protocols and subsequent studies.

I am proud to represent an Administration that has focused the highest levels of Government research on the health of Vietnam veterans.

As you know, after almost ten years and the expenditure of $90 million on scientific research of veterans by several agencies, we can now share with you the results of peer reviewed studies which will give us, the Congress, and Vietnam veterans cause to be reassured that their service in Vietnam and possible exposure to Agent Orange are not resulting in significant adverse health effects except psychological problems.

The Veterans' Administration, the Department of Defense, United States Air Force, and Centers for Disease Control will provide you with details of the status and findings of the key studies over which the Agent Orange Working Group has had oversight. The protocols for each of these studies and the subsequent conclusions, where available, have undergone thorough scientific peer review. They are:

The DOD Ranch Hand Study; that is, the United States Air Force study;

The CDC Vietnam Experience Study;

The CDC Study of Selected Cancers;

The CDC Agent Orange Study;

The VA Mortality Study; and other related studies.

The key point I wish to make today is that in the studies which have come to conclusion, we are seeing no cause-effect relationship between service in Vietnam with possible exposure to Agent Orange and adverse health.

The studies concerning the ground troops show no increase in dioxin levels in these troops. Scientific evidence does not support the claim that major increases in ill health are caused by exposure to Agent Orange. As you will hear in other testimony, it does not now appear that the average Vietnam veteran is at risk due to Agent Orange exposure.

We are not saying that no one was exposed in Vietnam. In fact, as Dr. Mason, Director of CDC will testify, we know that special groups whose occupation brought them into frequent contact with Agent Orange, such as Ranch Handers do have higher levels of dioxin in their blood.

The Centers for Disease Control's Morbidity and Mortality Weekly Report of May 27, 1988 indicated that of the 147 Ranch Handers examined, 62 percent had TCDD levels higher than 20 parts per trillion, that they had a mean serum level of 49 parts per trillion, and that the five highest had as much as from 201 to 313 parts per trillion.

While 20 parts per trillion is a generally accepted level in the general population, even after the most intensive physical examination, these, so far, have shown few ill effects, and they continue to be carefully monitored.

For the majority of Vietnam veterans, it is correct to say that, other than some problems related to stress, it does not now appear that they are at risk due to Agent Orange exposure. I, therefore, take the position that it is not sound public policy to make sweeping presumptions which appear to be based on frustration or the lack of scientific evidence to support desired conclusions.

The Government of Australia, as was mentioned in the earlier testimony, established a Royal Commission some years ago to examine the entire question of Agent Orange exposure relative to the Vietnam service of their troops, and they are examining the issue. In a 22-item telegram we received from our embassy in Australia last week, it was reported to us that the Minister for Veterans' Affairs addressed Parliament on May 19, 1988 on the conclusions of their Royal Commission which have been evaluated by their National Science Institute or Council.

The conclusions that they reached are almost identical to those of our own exhaustive studies and are similar in result with regard to stress, birth defects, and exposure. Their emphasis is well stated in the summation:

"The Government believes that too many Vietnam veterans' lives have been disrupted by fears about Agent Orange and other chemicals. In endorsing the view that any exposure of Australians to chemical agents in Vietnam would be unlikely to cause long-term adverse health effects, the Government in no way steps aside from its commitment to help veterans."

The U.S. News and World Report of May 23, 1988 said it best when it quoted Mary Stout, President of Vietnam Veterans of America, saying:

"The CDC Vietnam Experience Study results prove the resiliency of most of those who went to Vietnam and returned. There is a certain strength from peoples' experience in war. It helps them to deal with the fact that they go through a lot of stress, and it helps them to maintain a family, a home, and a job."

I regret that I have another meeting, but Dr. Mason, Dr. Hart, and Dr. Houk are here and have the expertise to answer the scientific questions that may be posed.

Thank you very much, Mr. Chairman.

[The prepared statement of Mr. Newman appears on p. 86.]

Mr. MONTGOMERY. Thank you, Mr. Newman.

Before you leave, let me ask maybe a question or two, because you made some strong statements here.

Your position as Chairman of the Domestic Policy Council Agent Orange Working Group is it is more of an emotional issue of the Vietnam veterans and there is no evidence that the Vietnam veteran is having any more ill effects from Agent Orange than other groups of the military that served overseas or here in this country?

Mr. Newman. Mr. Chairman, the exhaustive studies to date, $90 million worth, show no cause and effect relationship between ill health and exposure to Agent Orange in Vietnam.

In the studies, there is some exception to psychological incidences. There is a slightly higher level of psychological incidences in the Vietnam veteran group that continue to be studied, but there are no physical ill effects that can be associated with exposure to Agent Orange in Vietnam.

Mr. Montgomery. Would you explain or maybe somebody will later on on the panel about the blood test breakthrough on the measuring of dioxin? Would that help us on solving these problems of Agent Orange? Would you care to comment on that?

Mr. Newman. Yes, sir. That is a very good question, sir. About a year ago, we were ready to bring to your attention a breakthrough in the ability to analyze the dioxin level in blood. We found a process, or a process was discovered, whereby parts per quadrillion could be determined in the blood level.

Just to give you an idea of what that means, if you stack a row of dimes from here to the moon, you could pick out a single dime. That is what it means when you say one part per quadrillion.

Well, with that ability, we went back to the drawing boards, so to speak, to make an even more exhaustive determination of the quantity of the dioxin level in blood of Vietnam veterans. Prior to that, we had to extract a sample of fatty tissue from the buttocks of the Vietnam veteran and a fairly substantial one. It amounted to about two tablespoons full which is a substantial amount of tissue so that it made it very difficult to obtain on a large scale and therefore to associate dioxin levels with these veterans.

However, with the blood sample we were able then to determine the parts per quadrillion. We went back to the drawing boards and continued to exhaustively study the situation, and we came to the conclusion even then that there is no cause and effect relationship with any of the physical maladies claimed by Vietnam veterans.

Mr. Montgomery. Any questions before Mr. Newman has to leave from the members?

Mr. Penny. Mr. Chairman, I have one question, and that has to do with the decision not to proceed with the CDC study. Do you want to give us a little background as to the process you followed in deciding to discontinue that?

Mr. Newman. Mr. Penny, that will be included in Dr. Mason's testimony as Director of CDC.

Mr. Penny. I can wait for him, then, and I don't have to hold you for that purpose.

Mr. Newman. Thank you, sir.

Mr. Penny. Thank you.

Mr. Ridge. Just two quick questions if I may, Mr. Chairman.

Mr. Montgomery. Mr. Ridge.

Mr. Ridge. You mentioned that 20 parts per trillion was "an acceptable level" or perhaps one that we might find if we took blood samples from everybody in this room whether they were in Vietnam or not or exposed to Agent Orange or not.

Is there a scientific standard of unacceptability?

Mr. Newman. Not yet to be determined, sir. The highest level of the top five that we studied, 301 parts per trillion, has not shown adverse health effects. So, it would be difficult to establish a level that was toxic.

Mr. **Ridge**. I want to follow up on this blood test where you are able to distinguish in one per—

Mr. **Newman**. Quadrillion.

Mr. **Ridge**. Quadrillion, that is what I thought you said. Could you advise me as to who developed this study or this technique and how readily available it is to determine dioxin levels? Say, for instance, for those who are on the Vietnam registry who claim they were exposed to Agent Orange?

Mr. **Newman**. This was brought to my attention by Dr. Houk about a year ago. I wish we could make the claim for the discovery. It was discovered in England, and that research was then brought State-side. The CDC was the only one that I knew of that had the ability then, to transfer that technology to the United States. I am not sure if that is true today or not, but we are certainly the pioneers in that ability.

Dr. **Mason**. There are several laboratories internationally that can carry out such studies, but they are difficult, and the cost of one determination is in the range of $1,000. They can be done but it is a slow and expensive process. In my testimony, I will be talking about studies that are being done to look at particularly exposed populations.

Mr. **Ridge**. Thank you, gentlemen.

Thank you, Mr. Chairman.

Mr. **Montgomery**. Thank you very much. We appreciate it very much all of our witnesses taking the time today. It is important. It is an issue that you can hear by the questions and by the earlier witness that it is very emotional, it is very involved, and we need to get your best knowledge of this situation.

Dr. Mason?

STATEMENT OF JAMES O. MASON, M.D., DIRECTOR, CENTERS FOR DISEASE CONTROL; ACCOMPANIED BY VERNON HOUK, M.D., DIRECTOR, CENTER FOR ENVIRONMENTAL HEALTH AND INJURY, CDC

Dr. **Mason**. Thank you, Mr. Chairman and members of the subcommittee. I am delighted to be here with Dr. Houk and Dr. Hart. Dr. Houk has been responsible for carrying out these studies, and I am glad to have him here with me.

We have submitted written testimony for the record, so I will today briefly discuss the reasons it was not possible to do the Agent Orange exposure study. I will provide the results of the Vietnam Experience Study, which simply compares veterans in Vietnam with veterans not in Vietnam. We are looking at anything that may have occurred there, rather than exposure to Agent Orange in that context. Finally, I will provide information relevant to pending legislation.

Let me start with the status of the Agent Orange exposure study. It was designed specifically to evaluate possible health effects of exposure to Agent Orange in Vietnam veterans. The implementation of that study was dependent on a scientifically valid exposure index based on information contained in military records.

Between 1983 and 1986, the United States Army and Joint Services Environmental Support Group and CDC attempted to establish such an index. However, the results were such that we finally concluded that a scientifically valid study based upon military records was not possible without an independent method of verification.

In other words, we tried "hits," we tried where people were, and where spraying occurred. We even went to veterans and asked them to tell us whether they thought they were exposed to Agent Orange or not.

As we looked at the data and subjected it to the critiquing of various groups, none of the groups felt that a scientifically valid study could be done based upon military records or the veteran's evaluation as to whether they were exposed.

Therefore, utilizing our successful methods to measure TCDD, a form of dioxin in blood serum, we conducted a validation study and looked at various groups that had been identified by military records or who identified themselves as being exposed to Agent Orange. We compared their blood levels with a group of veterans that did not serve in Vietnam—that was the validation study.

The TCDD levels among the 646 Vietnam veterans were found to be similar to levels among 97 non-Vietnam veterans. I don't know if you can see that chart, but here are the 646 veterans, and that is where their TCDD levels fell. Here are the 97, and you see where their levels fell, and you notice there are two individuals among those that were thought to be highly exposed in Vietnam who exceeded 20 parts per trillion. Among the non-Vietnam veterans, none exceeded 20 parts per trillion.

So, among the Vietnam veterans that on the basis of self-reporting or military records were thought to be the most highly exposed, we only found two that really were above what you would expect to find in a normal population.

To go forward without having a valid exposure index might provide information that was biased against veterans or it might provide information that would be biased against the United States Government. In other words, you have no science base unless you can validly demonstrate exposure.

The only way that we could do a Vietnam exposure study would be to examine enough veterans to get a cohort of about 2,500 that we know were exposed. The cost of examining those veterans—possibly as many as 800,000 would have to be examined to get a cohort of 2,500—would create an expenditure somewhere in the range of $1 billion just to get the cohort to do the study.

Based on that, I think you can understand why the OTA and the Science Panel of the Agent Orange Working Group and others said don't do it. There are other studies that are being carried out—the NIOSH study of occupationally exposed workers, the Air Force health study of those who were involved in spraying that we know were exposed—which will give us the information that you would get after you spent your $1 billion.

At the time the validation study was being conducted, CDC was measuring TCDD levels on participants in two other studies, the U.S. Air Force and the CDC studies. Many of these individuals have current levels of TCDD greater than 50 parts per trillion.

This data is the Air Force Ranch Hand group, and you notice that if my finger on the chart is about at 20 parts per trillion, you can see that the Ranch Handers that were actually involved in the handling and spraying, and were obviously exposed, go clear up to 300 parts per trillion, and that data is based on serum that has been drawn within the last year and a half.

Therefore, we know that if you were heavily exposed, you still would be expected to have high TCDD levels today. We are working with the Air Force and with the National Institute for Occupational Safety and Health to follow groups where we do know blood levels to see what happens. I think it is very important that we have the results of those studies.

Now, let me move to the Vietnam Experience study. This was designed to evaluate possible health effects of the general Vietnam experience by comparing the health status of a cohort of male U.S. Army veterans who served in Vietnam with a cohort of male Vietnam-era veterans who served elsewhere.

This was initially studied with three main components: mortality assessment, telephone interviews, and medical and physiological examinations. Based upon the interim analysis of the data and the experience of the Air Force Health Study which involved the acquisition of birth records, CDC added a birth outcome validation component and a semen analysis component to the Vietnam Experience study.

With regard to the mortality assessment, this study has been reported previously. We have recently completed ascertaining the cause of deaths from the date of discharge through 1986. With the exception of the first five years following discharge from military service when the excess mortality was due mainly to external causes, Vietnam veterans continue to have a similar rate of all-cause mortality compared to non-Vietnam veterans.

Complete cause of death analyses, which includes the additional years 1984 through 1986, should be completed in August of this year.

The morbidity findings of the Vietnam Experience study—in our written testimony is a summary table—Table D. It shows the significant findings from the morbidity component of the Vietnam Experience study. Hundreds of observations were made, and these in attachment D are the only significant findings from this component.

Just a word about the components. The telephone interviews with nearly 18,000 randomly selected veterans revealed a broad similarity between the two groups in terms of current demographic and social characteristics such as education, income, employment rates, and marital status.

Although the study is not large enough to evaluate risk of specific types of cancers, the two groups were similar in the total reported number of physician-diagnosed cancers. I will comment specifically on non-Hodgkin's lymphoma later.

CDC is conducting a selected cancer study to evaluate risk for certain cancers which have been identified in the scientific literature as possibly associated with industrial or occupational exposure to phenoxy herbicides or chlorophenol and their dioxin contaminant.

The Vietnam veterans reported more problems with impaired fertility, yet both groups reported fathering the same average number of children. The Vietnam veterans also reported more birth defects and other health problems among their children. However, these reports were not verified by information contained in birth records.

In the medical and psychological component, we invited a random sample of approximately 40 percent of the interviewed men for comprehensive physical, psychological, and laboratory examinations. Physical and laboratory examinations showed few current differences between the two groups despite the many differences elicited by telephone interview.

For example, there were many large differences in reported skin problems, but on examination, all skin conditions, including scars from possible past chloracne, were found with similar frequency.

Psychological examination of the men who were examined was done through standardized interviews and questionnaires. Although most men in both groups fell within normal limits in these evaluations, certain psychological problems, primarily alcohol abuse or dependence, anxiety, or depression were more prevalent among Vietnam veterans than non-Vietnam veterans.

Of significance here is that although alcohol abuse or dependence was higher in the Vietnam veteran group, illicit drug abuse or dependence as defined by American Psychiatric Association criteria at the time of examination was not different between the two groups. About 0.5 percent of each group fell into this latter category.

Analysis of combat-related post-traumatic stress disorder showed that about 15 percent of Vietnam veterans reported ever experiencing symptoms which met diagnostic criteria of this disorder. These diminished over time, but 2.2 percent had still experienced an episode of post-traumatic stress disorder during the month before our examinations, up to 20 years after their service in Vietnam.

Overall, hundreds of physical health items were evaluated as part of the examination, including over 100 laboratory tests. For most items, no statistically significant differences were found between the two groups.

The most noteworthy differences were an increased proportion of Vietnam veterans with hearing loss, the presence of occult or hidden blood in stool, evidence of past infection with hepatitis B, lower sperm concentrations, and a lower average proportion of morphologically normal sperm cells.

The hearing loss is consistent with several studies of Army troops which show that exposure to military noise resulted in hearing impairment. Similarly, the higher prevalence of past hepatitis B was to be expected, because this disease was endemic in Southeast Asia.

The small increase in blood in stool and the sperm findings are unexplained. The sperm differences did not have an influence on the number of children fathered or on birth defects.

With regard to reproductive outcomes, although Vietnam veterans reported during the telephone interview more adverse reproductive and child health outcomes than non-Vietnam veterans, the children of Vietnam veterans were no more likely to have birth defects, all types combined, ascertained by hospital birth records, than were the children of non-Vietnam veterans.

These results are consistent with the findings of three major epidemiological studies, the Australian birth defects study, the CDC birth defects study, and the Air Force health study which were all conducted since 1981. In addition, the recently published study of birth defects in Seveso, Italy which was contaminated by TCDD in 1976 also found no increase in birth defects.

With regard to specific medical conditions relating to pending legislation, I am aware of pending legislation proposing that lung cancer, non-Hodgkin's lymphoma, and certain undefined immunological deficiency syndromes be considered as compensable in Vietnam veterans. In presenting the data in these areas from the Vietnam Experience study, I want to caution that the number of specific types of cancer are too few for drawing conclusions.

For non-Hodgkin's lymphoma, seven confirmed cases were identified in the Vietnam group compared to one confirmed case in the non-Vietnam group. Also, one confirmed lung cancer case was identified in the Vietnam group compared to two confirmed lung cancer cases in the non-Vietnam group.

These numbers differ slightly from those reported during the May 12, 1988, Senate hearings and represent the current data from the Vietnam Experience study based on the recent completion of medical record reviews. Additional cases may be identified in future mortality updates of these cohorts.

Additionally, we tested all the examined men for cell mediated immunodeficiency and laboratory assays of T and B lymphocytes and found no evidence of any differences between the Vietnam and the non-Vietnam groups in these immune system measurements.

Specific problems or lack thereof associated with Agent Orange exposure need to await the findings of the Air Force Health study and the NIOSH Production Worker study. Both of these studies will have exposure determined by serum values of TCDD.

In addition to the articles just published in the *Journal of the American Medical Association,* CDC is publishing a multi-volume monograph of the methods and results of the Vietnam Experience study. I am submitting at this time the first volume which is a synopsis of the study that expands on the published reports in the *Journal of the American Medical Association.* In addition, I am submitting the detailed analyses of the validation study to the committee.

(The material referred to above is retained in Committee files.)

Dr. MASON. That concludes my testimony, and we will be happy to answer any questions the subcommittee may have.

[The prepared statement of Dr. Mason appears on p. 92.]

Mr. MONTGOMERY. Thank you very much for that detailed information that you have given us, and I thank the other two witnesses for being backup for you.

Dr. Mason, I guess, basically, as I interpret it, from the technical viewpoint, you were saying almost the same thing that Chairman Newman was saying that there is really no hard evidence that Agent Orange and dioxin causes certain types of diseases in the Vietnam veterans?

Dr. MASON. That is absolutely correct.

Mr. **Montgomery**. Would it be unfair of me to ask you to give us the percentage figure of how far your study has gone, 90 percent, 50 percent of evidence that there is no exposure involved? Is that reasonable?

Dr. **Mason**. Our Vietnam experience study is basically finished except for following up over time, and we will continue to do that with the support of the Veterans' Administration on Vietnam Experience Mortality. We still have some records on the morbidity confirmation that we are looking at at the present time, and those will be available by this summer.

The study that is not completed is the special cancer study, and we have agreed, as I said in my letter to you on the 20th of May, to see whether we can at least do some preliminary evaluation of that data. We are not sure that it will be scientifically valid, but because it may provide additional data on non-Hodgkin's lymphoma, we are going to try to look at that, but that will require another three-month period.

However, the results of the full special cancer study will not be available until late in 1989, and will not be published until 1990.

Dr. Houk would like to respond.

Mr. **Montgomery**. Okay.

Dr. **Houk**. With regard to the Vietnam Experience study—it is frequently said that the study was negative and there are no positive findings. I don't think that is a true statement, and that is not what Dr. Mason said.

This was a random sample of Army enlisted people who served in Vietnam, and our best estimate is that that is about 2 million people. The most significant finding, in my view, Mr. Chairman, is that 2.2 percent—not an insignificant number of the 2 million Vietnam veterans—had an episode of post-traumatic stress disorder within a month of the time we examined them, or 20 years after they served in Vietnam.

This is something that needs to be addressed, and they need help.

Veterans are remarkably productive members of society. The figure that Dr. Mason gave of less than 0.5 percent in either group who are current drug abusers is far less than what we find in the general population. If you look at the things that we presented, over 60 percent of the men that are married are still married to the same wife. They have a good quality of life. There are a few who have some psychological problems, but, basically, they are doing, as a group, very well.

Mr. **Montgomery**. Doctor, what you are saying, I believe, is that there have been more psychological problems, which I can understand, from having the tests and the publicity on Agent Orange than actually there has been proof that the Vietnam-era veteran has a danger of coming down with cancer.

Dr. **Houk**. Yes, but I think also in addition to that, combat is a stressful situation, and we do not have data to compare the psychological effects found in the Vietnam study with those of the Second World War and Korea, as we do with mortality data. The only data we have were on prisoners of war of the other conflicts.

Mr. **Montgomery**. Thank you. Let me ask one other question, and then I will yield.

With non-Hodgkin's lymphoma, part of the selected cancer study, it has been suggested that that part be taken out of the selected cancer study and, therefore, you could complete the study earlier. Is that logical?

Dr. **Mason**. I mentioned that we will look at that data. The selected cancer study is carried out through contracts with major tumor registries in the United States, and we are getting the tumors which have at least theoretically been associated with exposure to Agent Orange. Because most of these are rare cancers or rare tumors, we go to the tumor registry and follow that to see if those people who are getting those tumors are Vietnam veterans. Then we have a comparison group so that we can compare the two groups.

To make the study valid, you have to have a certain number of these rare cancers, and that is why it takes time to accumulate enough cancers so that you get statistical significance when you analyze the data.

We are going to look at the data to see whether there may be something there at this early stage, but, generally, we haven't accumulated enough cancers to expect statistical differences even though they might exist if we followed this longer.

Mr. **Montgomery**. Charlie Stenholm and then Tim and then you, Lane.

Mr. **Stenholm**. Thank you, Mr. Chairman.

Dr. Mason, what is the scientific basis of establishing that 20 parts per trillion is a generally acceptable level of dioxin in the general population?

Dr. **Mason**. We don't want to say that that is a normal level, but we simply have analyzed groups of people that have the kind of exposure that you or I would have. For example, we started by asking medical examiners throughout the United States that were doing autopsies on people that had died through trauma, automobile accidents, et cetera, to get a general segment of the population. Then, we have looked at non-Vietnam veterans and other groups.

We find that most of them have a range of about 5 to 20 parts per trillion in their blood. That is what you would expect to find in people who were not specially exposed, occupationally or in some other way.

Mr. **Stenholm**. Do you have an experience to show what you can expect if you are at 200 level, 300 level, 400 level in the general population?

Dr. **Mason**. You don't find people with those levels in the general population unless there was some additional exposure, occupational or otherwise. The point is, when you find someone with exposure in that range, you want to find out what they have been doing that isn't what the general population has been doing.

Mr. **Stenholm**. Along that line, would there be any value in performing a study of the health effects related to Agent Orange exposure in small groups such as the chemical corps workers where there is evidence of substantial exposure? Would you recommend this in addition to testing the blood of Ranch Handers?

Dr. **Mason**. We are doing that. The National Institute for Occupational Safety and Health has a cohort of over 5,000 individuals that were exposed to dioxin as a result of the production of various chemicals. Dr. Houk is doing blood determinations on that group.

We know that many of them have elevated levels, and very careful cohort studies are being conducted of these occupationally exposed groups as well as working with the Air Force on their health study.

Mr. STENHOLM. When might we expect the results of these studies?

Dr. MASON. We are talking about results that will be coming along—it will be fiscal year 1990 until those studies would be completed.

Dr. HOUK. These are determinations now based upon the half life value in the high TCDD level people of the Ranch Hand study and in the NIOSH study. Also, we recently were in Germany where an industrial accident happened exposing production workers. At the time of heavy exposure, the levels are between 3 and 5 parts per billion as opposed to per trillion.

So, these people in the Ranch Hand and the NIOSH studies were very heavily exposed. If there are adverse effects of this agent in humans, it should be fairly evident to see in these two population groups.

Mr. STENHOLM. Dr. Mason, you mentioned in your testimony that there have been criticisms of the way that CDC tried to classify individuals with respect to exposure to Agent Orange. What specific suggestions have been made for alternative ways to classify exposure and what specific suggestions have been made by the New Jersey Agent Orange Commission?

Dr. MASON. I will have Dr. Houk respond.

Dr. HOUK. The criticism of how we selected people for the Ranch Hand study is because part of the selection process used what is called the "Hit" model. That is within 2 kilometers of a sprayed area for 6 days.

However, if that were the only way that we measured exposure from the military records, that criticism would be very valid. It is not, however. We used that method. But we also looked at whether they were ever in an area that has been sprayed within the previous six days. Whether they served at any time in areas of Vietnam that were the very heaviest sprayed. Also where there was perimeter spraying with known Agent Orange and with unknown compounds. We looked at the veteran's perception of his being exposed, and the perception of his having adverse health effects from that exposure.

None of these parameters showed any difference.

I might also point out that the people we examined in this study were the ones that most likely were to have been exposed. We chose veterans who served in the core regions of Vietnam where Agent Orange was most heavily used and who served during the years that it was heaviest used. If we were unduly biased, it was toward exposure, and we found no evidence of exposure in the ground troops.

I might point out, if the people were occupationally exposed, that is, handled Agent Orange, there is now evidence both from our study, from the New Jersey study and the findings from Germany that we can identify those people now.

Dr. **Mason**. I just want to say that our staff wanted to do the Agent Orange exposure study, and I don't believe there is a stone left unturned in terms of trying to identify people who were exposed. As I mentioned in my testimony, the only way we know that we could go about that at this point in time is just to take those that are thought to be at highest exposure and then screen enough by blood testing so we could finally develop a cohort big enough to do a study.

However, the expense involved in that is so great. While we have the Air Force study going on and the NIOSH study, we don't need to go to that expense to study a cohort of exposed people to see if they develop disease as a result of dioxin exposure.

Dr. **Houk**. Could I also add, Mr. Stenholm, it is not only the expense, but it is the time. This is very labor intensive work. We can only do in our lab 50 samples per week. There is only one other lab in the world that does this technique, and they are slower than we are. They haven't automated quite as much, as we have.

If you have to screen 800,000 at 50 per week, you can see that the weeks will very rapidly tick by, and you will never get it done.

Mr. **Stenholm**. Thank you.

Thank you, Mr. Chairman.

Dr. **Rowland of Georgia** (acting chairman). Mr. Penny?

Mr. **Penny**. Thank you, Mr. Chairman.

Dr. Mason, there are health care professionals who say that the effects on animals of exposure to dioxin are pretty clear-cut and identifiable. Why is it that you feel we can't translate that into an obvious effect on humans as well?

Dr. **Houk**. With some chemicals, Mr. Penny, the effects are rather consistent across species, or within the same species, or in different species. Or the effects get worse, or increase or decrease as one goes up and down the list, then that becomes a reasonable presumption.

Unfortunately, with the dioxins, these are very animal-specific effects. In other words, the effects within the species vary. A guinea pig is tremendously sensitive, but a hamster is relatively resisistant, and there is no consistency that one can have of any patterns. You just can't use that as a predictor of disease in humans.

Mr. **Penny**. What about the experience we had at—what was that town in Missouri?

Dr. **Houk**. We have people in the Missouri population who were heavily exposed to dioxin. There have been no adverse health effects. We have studied them, although it is a small number of people, fairly intensely and have found no evidence of adverse reproductive outcomes, no evidence of immunologic disease, and no evidence of any other disease were found in very extensive studies.

Mr. **Penny**. Pardon me for not knowing, but have we as a matter of public policy established a procedure to continue to monitor that population? I know those folks have been moved out and who knows where many of them are now, but are we tracking that population group and conducting ongoing tests?

Dr. **Houk**. All of this population group is on a central listing in the State of Missouri, and the Agency for Toxic Substances and

Disease Registry is looking at putting them on a national registry to see if that will be useful in the future.

Mr. **Penny**. You know, I think that would be. It seems to me here we do have a bunch of folks who received significant levels of exposure, and if there are health problems that develop down the line, it is a group that we ought to have plugged into our national research structure.

Dr. **Houk**. This is being done by the Agency for Toxic Substances and Disease Registry. There are problems, however, with such activities. There are a lot of ethical problems, also people not wanting to be constantly reminded, the inability and difficulty of keeping track of people every year and trying to do this without intruding on their rights to privacy.

Mr. **Penny**. Can't we screen that down with some kind of a general mailing asking for folks within that population to agree to be annually monitored?

Dr. **Mason**. I am also the administrator of the Agency for Toxic Substances and Disease Registry. Last week, our Board of Scientific Counselors was considering this very issue as to whether there was enough potential for scientific return. The State of Missouri, with our help, is maintaining that listing, and we are now looking at the scientific feasibility of going further with that.

We also want to make sure that we can't get the same results from the NIOSH study which is already set up and where we are investing a lot of time and effort. If the scientific counselors that are evaluating that issue make a recommendation that this would be worthwhile in terms of scientific information on health policy, then we will go ahead with the registry.

Mr. **Penny**. Well, I would hope that you would pursue it. I am not a scientists, so I can't give you the advice you are going to get from your scientific counselors, but I think common sense tells us that we have an opportunity here, and I would hope that you would use it.

The New Jersey study differs with some of the conclusions that CDC has reached. Why do think a State study on Agent Orange has come up with different conclusions?

Dr. **Mason**. I don't think you will be hearing from them that we basically differ. They found Vietnam veterans who had elevated dioxin levels, we did, too, and the Air Force has.

What I think we have both found is that veterans in Vietnam in general don't have elevated TCDD levels while, if you can test persons who had exposure as a result of their having been involved in spraying or some other thing, indeed they do have elevated levels. I think that is a consistent finding in the Air Force, CDC, and New Jersey studies.

Mr. **Penny**. Didn't the levels or the numbers involved differ somewhat between their study and the conclusions you have come up with at CDC?

Dr. **Houk**. No. The data are very consistent. Fortunately, the two laboratories, the one in Sweden used by New Jersey and our laboratory, get very consistent and similar kinds of results.

They showed in their smaller numbers of persons studied than we did with our larger numbers for the Air Force that if the veteran is occupationally exposed, that is, handled somehow the herbicide, that person has higher levels of dioxin in their body now, and we can still find it 16 years after their service or 20 years after their service.

Mr. **Penny**. Mr. Chairman, I have no further questions.

Dr. **Rowland of Georgia**. Thank you, Mr. Penny.

Mr. Evans?

Mr. **Evans**. Thank you, Mr. Chairman.

Dr. Mason, I understand the Vietnam Experience study found that 7 of the Vietnam veterans had non-Hodgkin's lymphoma and that only 1 veteran who had not served in Vietnam had this disease. I understand that all of these cases have been confirmed and that several previous studies have also suggested this possible causal link between dioxin exposure and non-Hodgkin's lymphoma.

How do you interpret these findings?

Dr. **Mason**. You are absolutely correct with regard to the number of cases, we found seven in the veterans with Vietnam experience and one in the non-Vietnam veterans. There is no way that the Vietnam Experience study looks at or can show any relationship of health affects to Agent Orange. It simply looks at Vietnam experience generally, and there are a number of things, including Agent Orange and dioxin, that could be accounting for that.

First of all, I have to say that this may not even turn out to be good significant data, and that is why we want to look at the sentinel cancers before we "make a call." It certainly is a trend that if it continues will at some time become significant, but at this point in time, it is not.

The other study is the study that was done by the National Cancer Institute, and this was done on agricultural workers that were using the herbicide 2,4-D. Interestingly, 2,4-D does not contain TCDD, the kind of dioxin that we have been looking at, but Agent Orange contains 2,4-D. It is a mixture of several herbicides.

What I am saying is that you can't take the seven to one comparison and declare, at this point in time that it is significant. It certainly is something that is going to have to be looked at very carefully.

The second point is we can't pin that down to dioxin and we can't pin it down for sure to herbicides. We are really getting that data from an experience study that included much more than Agent Orange. It included anti-malarial medication and a whole series of other things.

Mr. **Evans**. You know, I can certainly understand your problems in scientifically establishing this causal link with the studies that you have surveyed so far, but I think you must also understand our frustration sitting here as policy makers and wondering just why in the world there is this disparity for whatever reason.

I guess another question I have with regard to the Vietnam Experience study report was in the Journal of the AMA. I understand that there was not a specific mention of the non-Hodgkin's lymphoma in that publication of that report. Is that correct, and why was that so if that is correct?

Dr. **Houk**. Yes. In the Vietnam Experience study, we stated early on that the study was too small to decide about these particular kinds of tumors. Therefore, we constructed a special study which is a selected cancer study that Dr. Mason mentioned which will be large enough to give a yes or a no answer.

Because of the real concern about non-Hodgkin's lymphoma and after the VA proportionate mortality study, we decided to go back through the interview process and "cast a very large net." If a veteran answered a question that could possibly indicate that he may have had a lymphoma or tumor, we went and got all of the medical records surrounding that individual.

Unfortunately, before we testified in the Senate, we didn't have all the records. They came in on the Wednesday after that testimony, and we got 3 cases in Vietnam veterans and 3 cases in non-Vietnam veterans. These are now confirmed. We could not have reported that to this committee or to the Senate committee any sooner. We reported it within two days of the time that we completed the analysis.

All of us who have dealt with this issue for a long time—herbicides and cancers—feel that—I don't like to use the expression "smoking gun"—but the area of non-Hodgkin's lymphoma is the one that all of us feel least comfortable with. That is the reason that we are putting a lot of effort into the special cancer study hoping that we can get a yes or a no answer out of that.

With regard to the 7 and 1 differential, the data is so shaky that we have advised people against doing statistical tests on that data. You can do statistical tests on everything, but if they are not biologically plausible, it doesn't make any sense to do.

However, you are right. This is an area that those of us that have been involved in the studies for a long time have the least comfort in saying we are relatively certain that there is no association.

Mr. EVANS. Thank you.

Dr. ROWLAND OF GEORGIA. Mr. Stenholm?

Mr. STENHOLM. Yes, I have one additional question.

You said that 2,4-D was present in Agent Orange, but Agent Orange was not present in 2,4-D? What about 2,4,5-T?

Dr. HOUK. Agent Orange is a 50/50 mixture of 2,4-D and 2,4,5-T. The dioxin contamination comes from the manufacturing process 2,4,5-T, the 2,3,7,8 which we are talking about. 2,4-D does not contain that particular dioxin. It contains four of the other dioxins which are very rapidly excreted and very much less toxic in acute animal studies of animal toxicity.

Mr. STENHOLM. No further questions right now. Thank you.

Dr. ROWLAND OF GEORGIA. I apologize for having been gone during most of your testimony. There are two or three things that I would like to ask you about.

Based on present scientific studies that you have, you have fairly well come to the conclusion that there might not be a great physical difference that exists between Vietnam veterans exposed to Agent Orange and the population in general, but you have somewhat come to the conclusion that there is considerable psychological difference between Vietnam veterans.

While it is difficult to reach a scientific explanation about psychological differences, could you elaborate on that any at all as to why you think that there may be this difference from a psychiatric standpoint?

Dr. MASON. Let me start with our mortality study, Vietnam veterans mortality versus veterans who did not serve in Vietnam. We found that there were elevated death rates in Vietnam veterans compared with non-Vietnam veterans during the first five years after their service, and these death rates were related to trauma, generally; homicide, suicide, accidents, and injuries.

Dr. ROWLAND OF GEORGIA. Could I interrupt you just at that point? I don't want to interrupt your train of thought, but on television recently, there has been an estimate of 100,000 suicides in Vietnam veterans. Do you have any particular information on that? Since you mentioned suicide, I was just wondering if you could elaborate on that at that point.

Dr. MASON. We don't know where the figure of 100,000 came from, but if we look at the difference in suicides between Vietnam veterans and non-Vietnam veterans and then extrapolate that back to the total population of servicemen that served in Vietnam, we would come up with a figure right around 9,000 excess suicides, and the confidence interval would be from about 6,500 to 13,000.

Although that is 10-fold less than the figure that you just cited, there is no question based upon the Vietnam mortality studies that we have done that there are excess suicides in Vietnam veterans as compared with non-Vietnam veterans.

Dr. ROWLAND OF GEORGIA. Was that in the first five years or was that after—

Dr. MASON. The first five years, and then after the five years, you no longer see differences in the two groups.

Dr. ROWLAND OF GEORGIA. So, at this particular time, there doesn't seem to be that difference, but there was in the first five years.

Dr. MASON. That is right, and in the area of mortality we can go back to Korea or World War II where other mortality studies have been done, and these findings in Vietnam are not unusual in the context of other studies on a five-year period after any war.

Dr. ROWLAND OF GEORGIA. I apologize for getting you off the track. If you can go back to the statement that you were—

Dr. MASON. I wanted to start by saying that differences in mortality seem to appear to be related to psychological factors. So, it is probably not surprising that when one begins to look at psychological and mental disturbance that you find changes in Vietnam veterans that do not occur in non-Vietnam veterans.

We found post-traumatic stress disorder occurring in Vietnam veterans. There was no such thing in the non-Vietnam veterans, by definition.

But alcoholism and alcohol dependence, depression—these things were significantly different in Vietnam veterans than non-Vietnam veterans.

Dr. ROWLAND OF GEORGIA. And we are still having that problem with the veterans. That is still there, isn't it? It is a problem that we need to be dealing with.

Dr. MASON. Absolutely, and particularly, as Dr. Houk said, with regard to the post-traumatic stress disorder. Slightly over 2 percent of Vietnam veterans had had such symptoms within a month of their examination.

Dr. Rowland of Georgia. Let me ask you this question very briefly. I know the store front centers where these veterans came to have been very successful, and there has been some attempt to shut these down and move veterans to hospitals for their care.

Based on information that you have so far, do you think that is a proper course to be taking?

Dr. Mason. We really can't make an assessment of that. We can tell you what is going on in these veterans, but as to the management—we can give you risk assessment data, but we haven't even looked at risk management, in other words, doing something about the problem.

Dr. Rowland of Georgia. The risk assessment—it seems to me that we could say it is more risky, at least from what I have learned, to try to move these veterans to hospitals rather than letting them continue in the store fronts. That is my own opinion, I guess.

Dr. Mason. And we just haven't even considered that part of the problem.

Dr. Rowland of Georgia. All right.

Well, let me thank you very much for being here this morning. I want to congratulate you, Dr. Mason, on the AIDS information booklet that CDC—I want to say that parenthetically that this is certainly a bad problem, and CDC has been supportive of the commission idea, to my knowledge, and that legislation is now in the Senate to follow up on the President's commission and seems to be stymied at this point over there.

I would certainly hope that it could be released, because we are going to continue to have to establish policy, it seems to me, with reference to AIDS, and we need to have some advice here in the Congress about how to do that.

Thank you very much for being here this morning.

Dr. Mason. Thank you.

Dr. Rowland of Georgia. Without objection, Dr. Mason, your full statement will be made a part of the record.

Other members and I will have written questions for you to answer, and we will submit those later in the week.

I would like to ask now Major General Alexander Sloan who is Deputy Surgeon General of the Department of the Air Force to come to the witness table.

General Sloan, thank you very much for being here this morning, and you may proceed in your own manner.

STATEMENT OF MAJ. GEN. ALEXANDER SLOAN, DEPUTY SURGEON GENERAL, DEPARTMENT OF THE AIR FORCE; ACCOMPANIED BY COL. WILLIAM WOLF, M.D.

General Sloan. Thank you, Mr. Chairman.

With your permission, I would like to have Dr., Col. William Wolf, the senior principal investigator in the Ranch Hand study, accompany me.

Dr. Rowland of Georgia. There is no objection.

General Sloan. I have submitted my prepared statement for your consideration and would like to offer some abbreviated comments.

Dr. ROWLAND OF GEORGIA. Your entire statement will be made a part of the record, without objection.

General SLOAN. Thank you, sir.

Thank you for the opportunity to present an update on the progress of the Air Force health study of personnel exposed to herbicides in Southeast Asia. Our study, based on a scientific approach, includes those who sprayed herbicides, the Ranch Hand group, and a group of matched comparisons. It is a planned 20-year research effort.

Our protocol was extensively reviewed by multiple scientific peer groups. The study includes detailed questionnaires and periodic clinical examinations by internal medicine, neurology, and dermatology specialists as well as psychological and extensive laboratory testing.

Participation in the study has been excellent.

To date, we have published four mortality reports and two morbidity reports, the most recent in October of 1987. All mortality reports have contrasted survival of all known Ranch Hands who have not died in combat while in Vietnam with matched comparisons. The overall death rate of the Ranch Hand group is nearly identical to that of the comparison group.

The 1988 mortality update is currently underway and is expected to be published this summer.

At this time, there is insufficient evidence to support a cause and effect relationship between herbicide exposure and adverse health in the Ranch Hand group. The study has revealed a number of medical findings that require continued surveillance.

In full context, the results of the study are encouraging evidence that the current health status of the Ranch Hand participants appears unrelated to herbicide exposure in Southeast Asia. However, we still cannot exonerate the herbicide.

Recently, a new method of determining dioxin exposure has been developed. This blood serum assay will provide an accurate measure of the current body burden of dioxin. This greatly improves our ability to calculate individual exposure levels.

A pilot study of 200 serum samples confirms clear and meaningful dioxin exposure did occur in the Ranch Hand group.

The ability to improve the estimated exposure index with the serum dioxin test is a major opportunity in the scientific evaluation of the Agent Orange issue. This new serum dioxin assay will provide an accurate measurement of the current body burden of dioxin. It should also be possible to estimate the half life of dioxin in humans.

Within the next two years, another morbidity report on the 1987 examination results, mortality reports, and an expanded birth defects analysis will be completed. We have analyzed the results of the first 5 years of our 20-year research study looking at the herbicide health question. Nearly 100 Government, academic, and industry scientists have guided and contributed to the study since its inception.

Our studies have not been able to establish a cause-effect relationship between adverse health and herbicide Orange exposure. However, our studies identified some issues that require further evaluation.

In conclusion, we feel the Air Force health study is the premiere federally funded herbicide related study underway. Its findings are important to our veterans and to their families. With your continued support, our work will continue.

I will be happy to answer any questions you may have.

[The prepared statement of General Sloan appears on p. 112.]

Dr. ROWLAND OF GEORGIA. I have just a couple of quick questions.

You mentioned the serum dioxin assay study. That is an extremely expensive test to be done to test the lipids in the blood for the presence of dioxin.

I have read that it might be helpful, rather than to titrate out to determine the exact level of dioxin, if we have some end point and we can do more of a qualitative rather than a quantitative analysis of dioxin in the blood. In other words, a person would have a certain amount of dioxin in the blood, and everything below that would not be considered significant. Everything above that may be considered significant and reportable.

Would it be helpful to be able to do that?

General SLOAN. I presume anything that would give you a direct measurement of whether a person had been exposed above a certain level of not would be helpful. However, in the assessment of certain clinical conditions for presence of disease, it would seem to me to be much more helpful to be able to quantify, that is, a 200 level versus a 40 level would be presumptive evidence that there would be more dioxin in the person's body that had been more heavily exposed at this time, and we would then relate that to the presence or absence of statistical differences between our Ranch Hands and comparisons and, presumably, the heavier exposure would allow you to draw conclusions more scientifically valid.

Perhaps Dr. Wolf might want to comment.

Colonel WOLF. Since the inception of our program, we had hoped to identify a target condition or a target disease and have been unable to do that. I think the availability of this assay may well allow us to do that and determine at what level of dioxin significant health effects might occur.

Without that assay, we are in a guessing game of sorts, making assumptions about how clean or dirty people worked, how much of the workload each person assumed, and how effective a worker they were. Those kinds of assumptions are inherent in any exposure index calculated from historical data.

This assay will allow us to avoid those sorts of assumptions and come up with a much more accurate assessment.

Dr. ROWLAND OF GEORGIA. Would it be much more expensive if you had a definite end point that you were trying to reach rather than trying to titrate the amount of dioxin?

Colonel WOLF. I think we could save money, but I think we are on much more firm scientific ground. We can categorize. When you categorize into four or five categories or one or two categories, you lose a lot of precision. When you have a continuous measure, your statistical capability is much more greatly enhanced.

Dr. ROWLAND OF GEORGIA. Let me ask you one other thing. In the 1987 Ranch Hand morbidity study, there was a subject of a technical report by Dr. Richard Albanese. Dr. Albanese's report was interpreted to be a criticism of the 1987 Ranch Hand study. Could you clarify that situation for us?

General **Sloan**. Sir, the technical report that you referred to authored by Dr. Albanese was not a 1987 related assessment. It was a relook at the same data, the same statistical information that was reported in the original Air Force morbidity report that was published in 1984.

It was a little different look at it. It focused on a literature review of animal data that we have heard previously from the investigators from CDC as to the difficulties in ascribing animal results to humans, in particular, in the area of dioxin, and it was the assessment of that author's opinion as to where one might look for adverse health effects if one were to look for such dioxin effects.

It was not part of the Ranch Hand study itself. It was basically an independent investigator's assessment of the circumstances dating clear back to 1984, did not take into account information that had been developed since 1984 that was published in 1987.

Dr. **Rowland of Georgia**. Thank you very much.

Mr. Evans?

Mr. **Evans**. I have no questions.

Dr. **Rowland of Georgia**. General Sloan, thank you both very much for being here this morning.

The next witness we will ask to come to the table is Dr. Michael Gochfeld who is co-principal investigator of the New Jersey Agent Orange Commission.

Thank you very much, Dr. Gochfeld, for being here, and you may proceed in your own manner.

STATEMENT OF MICHAEL GOCHFELD, CO-PRINCIPAL INVESTIGATOR, NEW JERSEY AGENT ORANGE COMMISSION; ACCOMPANIED BY WILLIAM LEWIS

Dr. **Gochfeld**. Mr. Chairman and members of the committee, I have prepared a testimony for the record which I would like to summarize. I am also accompanied by Mr. William Lewis of the New Jersey Agent Orange Commission in case there are questions regarding commission activities.

Dr. **Rowland of Georgia**. Without objection, your entire statement will be made a part of the record. We are delighted to have both of you.

Dr. **Gochfeld**. First, I should tell you a little bit about myself. I am on the faculty of the Robert Wood Johnson Medical School, formerly Rutgers Medical School, which is part of the New Jersey State system.

I came to New Jersey to be director of the New Jersey State Department of Health where I was director of Environmental and Occupational Health for several years before coming to the university. So, I am speaking largely as an academic researcher, partly as a clinician, and also partly with a history of having been an administrator and regulator for a few years.

It is no surprise that the Agent Orange veteran issue has become highly politicized, and as a scientists, I am going to focus attention on the scientific issues insofar as possible, although it has become difficult to separate them.

I also spend a lot of time dealing with risk assessment and the process of risk communication, and we teach what I believe to be the first course—now there are several others—to public health professionals and toxicologists in environmental risk assessment.

We recognize there that as difficult as it is to get a handle on risk, it is even more difficult to communicate that risk to the public. One of the things you learn as a State health person is that the last thing you want to do when you have a community that is concerned about its health is to come in and brush it aside and say no problem, we are taking care of everything.

I think that was the climate in which the Agent Orange Commission undertook its research five years ago, and I am glad to say from what we have heard today that that climate is largely changing. Research is going on and is being taken seriously.

I think there are a number of true and important statements. The average veteran in Vietnam probably was not exposed for learning now. We don't know exactly what proportion were engaged in operations, but we know that it is only a small part of the veteran population. Whether it is 10 or 50 percent I don't think anyone can guess at this point.

That has important ramifications for interpreting epidemiologic studies which I would like to come back to.

We have also heard several of the earlier speakers say that all of the studies done so far show no cause and effect relationship between dioxin and health effects, and I don't think that is what the CDC speakers or General Sloan were just saying. I think they were saying very carefully that the evidence is not sufficient.

So, it was in this climate that New Jersey began a study of trying to understand whether there was evidence of exposure and how we could identify exposed groups.

Did you have a question?

Dr. ROWLAND OF GEORGIA. I wanted to ask you—you said health effects. Now, you were talking about mental health or physical health or health generally?

Dr. GOCHFELD. I was talking about the global question. I think that there is very clearly separate subsets of health problems, and I think also there are very clearly separate subsets of veterans. I will come back to that in my testimony.

Dr. ROWLAND OF GEORGIA. I apologize for interrupting your thoughts.

Dr. GOCHFELD. Not at all.

One of the things that in 1984 we planned was a small study consistent with a State funded enterprise to determine whether we could really recognize high levels of dioxin—TCDD specifically, but we were also looking at other dioxins as well—in the blood and fat of veterans, and I think it was the aggressive stance that the commission took at that time that this was not only feasible but desirable which encouraged other agencies to also look at blood.

The laboratory of Dr. Christopher Rappe in Sweden developed that technique. They knew it was feasible. They convinced us it was feasible. The CDC invited Dr. Rappe to be a consultant to help them set up their dioxin laboratory, and I think it is very fortunate that both agencies were using very comparable facilities, very comparable methods, and I think that provides credence to the very comparable results that emerged.

The New Jersey study which is included in the attachment to the testimony was published in the March 18 issue of the Journal of the American Medical Association. This is a report on phase one or point man one.

We took 10 veterans—this is going to sound like a minuscule sample compared to what we have heard about from the Federal studies, but Federal studies should be on a larger scale. This was a sample of 10 veterans whom we had every reason to expect were highly exposed based on a detailed questionnaire which they provided and 10 Vietnam veterans whom we had every reason to believe had negligible exposure, that is, they were based in major urban areas or on large bases.

We tried to get 10 veterans who were Vietnam-era veterans who hadn't gone to Southeast Asia. We were only successful in getting 7 of the latter category, and I think that is a flaw in the study, but as it turned out, it was not a critical flaw.

The men were brought into a hospital where they underwent three and a half days of intensive medical, psychological, and laboratory testing during which they received a fat biopsy and a large blood sample. We are talking about close to a unit of blood that was obtained.

The fat and blood were coded anonymously by a referee over whom neither we nor the analytical laboratory had any control, and this assured, as far as we were concerned, that the results were beyond reproach. They were sent to Dr. Rappe's laboratory in Sweden, and when the entire study was completed, the result were decoded.

What we found was the following: Of the 10 heavily exposed veterans—these were Ranch Hand types of people, herbicide handlers for the most part—compared to their 10 matched non-exposed Vietnam veterans, in 9 out of the 10 pairs, it was the exposed veteran who had the higher level of TCDD in their fat.

When we looked at the blood, the results were less clear. One of the analytical tests was unsatisfactory, so we could only look at 9 pairs, and in 6 out of 9 cases, it was the exposed veteran who was higher, and the other 3 were close to a tie.

The results of the fat are clearly statistically significant, that is, there is less than 1 chance in 100 that that could be due to chance alone. The results for the blood were marginally significant but compelling none the less.

What added credence to this was that we also looked at 12 other dioxin and dibenzofuran compounds in the blood and fat, compounds which we all are exposed to at very low levels because they are present in some fish and they are present in fallout from incineration or such. It was only 2,3,7,8-TCDD that showed the elevation in the exposed men. All the other compounds were comparable in the exposed and what we could call the control group.

The importance of this is that when you are looking at Agent Orange—the dioxin in Agent Orange is 2,3,7,8 almost exclusively—so the prediction is that if any one is going to be elevated, it is going to be that one. And what lends credence to the Vietnam exposure issue is that that was the only one that was elevated.

So, we are dealing with something that is herbicide related and not related to general life experience.

You have heard Dr. Mason say that the results of the New Jersey and the CDC studies agreed, and I think that is very important. They are remarkably close, almost too close if you were going to predict it.

We both got about 40 parts per trillion of dioxin in the exposed population and about 5 in the background, non-exposed population. We both found very high correlations between blood and fat, and that is very important, because it also lends credence to our ability to rely on the blood test as a measure of exposure.

The New Jersey study is not primarily a health effects study. We looked at the health status of these veterans largely to providemay be of value to them. Regrettably, many of them brought us sad tales of the treatment they had received in the VA Agent Orange examinations. So, one of the offerings or the inducements was that we would give them a comprehensive examination with their results, with referrals for evaluation should that be indicated.

So, it is not a health effects study. We are going to look at the health effects data, and we will certainly report on it however that turns out.

It is primarily an exposure study, and it establishes a methodology for using a blood test as a surrogate or as an indicator past exposure.

Questions have been asked about what it means to have a level of 200 or 300. Our highest level was about 200. The highest level in the CDC study was about 300, again, really quite close agreement.

If we take a half-life which the CDC got of an estimated about 7 years, then about 14 years earlier, these people would have had four times as much as they do today. The implications of that can only be guessed at. That will be enhanced by the very important NIOSH study looking at occupationally exposed people where we anticipate that they will find and I have heard that they have found higher levels than were found in veterans.

Now, I wanted to comment—the question was, how did one get the 20 parts per trillion cutoff? We independently of CDC looked at our data and came up with a 15 parts per trillion cutoff. Whichever you use it is really not material. It basically says that if you look at the population at large of unexposed people, people such as you and I who eat fish occasionally or who may live a few miles down wind from an incinerator or an industrial smoke stack or what have you, we will have about 5 parts per trillion on the average, maybe 10 or 14, but not 25, and I think, again, the two studies agree on that.

We can use a cutoff as a way of identifying exposed people. We will miss some exposed people, because some of the people whom we think were exposed don't have levels that high, but that classification is not bad, because what we are interested in is the impact of levels of TCDD on health.

The species issue that we have all been grappling with is a critical one. I work in a department that has a lot of toxicology. We rely heavily on extrapolation from animal studies.

I must agree with Dr. Mason that, not uniquely but certainly clearly in the case of TCDD, the extrapolation is not clear, because among rodents alone, guinea pigs versus mice versus hamsters, there are substantial orders of magnitude difference in sensitivity.

I have no doubt from the data that has been presented by the various groups that the human being is not as sensitive as a guinea pig. If we were, we would have found clear health effects a long time ago.

I don't know if we are resistant as a hamster. Nobody has that information. I think some of the studies that we have heard about, some of the studies that perhaps may be undertaken, may address that issue of just how sensitive the human species is.

One of the concerns that I think has to be addressed—and the CDC voiced it very clearly in the three papers that were recently published in the Journal of the American Medical Association—is that when you look at veterans as a whole, you can't draw inferences regarding herbicide exposure, because only a fraction—we don't know what that fraction is—but only a fraction of that population is an exposed population.

So, any effects that might occur in that sub-population are diluted by looking at a much larger sample.

I think the CDC has been very clear in pointing that out in their papers. I think that some people who read those papers may not be so clear in making that distinction.

So, if one wants to connect health effects, wants to look for a connection, one has to more precisely identify exposure.

I think, by the way, that the veterans study is a very important study without regard to Agent Orange, because I think this is a population that had other problems besides herbicide exposure.

I have ended up, I think, being an advocate for a blood test, and if I may take the liberty of addressing the question you asked before, I think that certainly from the figures that Dr. Mason presented of having to screen 800,000 people to come up with 2,000 that they could study, if those figures are appropriate, a screening test, if it were developed or when it is developed, because I am sure it will be developed some day, would be useful and probably less expensive.

I think, however, that the evolution of laboratory testing for any substance is such that the costs will come down. They have already come down from an estimate of $2,000 to $2,500 that was given to us in 1984 to about $1,000 exclusive of shipment which we are paying today. That is approximately the same as CDC has estimated their own costs to be.

I cannot believe that as these methods are perfected the price won't come down as they have for all other organic analyses, pesticides, hormones, and the like. So, a price on the order of $300 to $500 may be realized before the end of the decade.

I also have to believe that wind of a large Federal contract in this area would certainly encourage the private sector to develop these methods at a competitive rate, hopefully without sacrificing quality control.

I think I will stop there. There are certainly many other things to talk about with regard to health effects, but since we are not doing a health effects study, I will leave that for other people.

Thank you, and I would be glad to answer any questions you may have.

[The prepared statement of Dr. Gochfeld appears on p. 126.]

Dr. **ROWLAND OF GEORGIA**. As you pointed out, the 10 veterans that you used have exposure. That was not a health effects study but an exposure study. I believe you said you threw out one of them and three were at about comparable levels and there were six left that had high levels?

Dr. **GOCHFELD**. And their partners. That is correct.

Dr. **ROWLAND OF GEORGIA**. Well, while it wasn't a health effects study, could you make a comment on the health of these six veterans that were left?

Dr. **GOCHFELD**. Because it wasn't a health effects study, we carefully excluded from the study people who had dramatic health problems. The unfortunate caricature of the Vietnam veteran as a hostile, angry, psychologically distraught person—we didn't get many people of that nature among our pool of participants, but if we did, they were not invited to participate simply because we had to be responsible for them for three days in the hospital.

Dr. **ROWLAND OF GEORGIA**. You deliberately selected people that were healthy then?

Dr. **GOCHFELD**. We deliberately selected people that were relatively healthy. That is correct. I don't think that is an unfortunate bias. It was important for what we set out to do.

Dr. **ROWLAND OF GEORGIA**. As you pointed out, you certainly can't extrapolate the results of laboratory animals to humans.

Dr. **GOCHFELD**. In the case of TCDD. I don't want to go on record with that as a general statement. I think animals are important.

Dr. **ROWLAND OF GEORGIA**. In this case, because guinea pigs are much more susceptible, but might there not be genetic differences between individuals that could make a difference?

Dr. **GOCHFELD**. There are most certainly. We know that with respect to the ability of individuals to metabolize organic chemicals. Some of us have more of particular enzymes than others. That is an area that is just being explored. Some very exciting work is coming down which may enable us to identify those people who will be more vulnerable.

Certainly, I think it is safe to say that no one has a handle on that with regard to TCDD, but your statement that there may be more vulnerable individuals is a real consideration, and when you deal with 2 million veterans or even if we dealt with 500,000 or 200,000 exposed veterans, even a small percentage of that may end up being a lot of people.

For example, figure the very small percentage of people who have PTSD now. If you translate that into real numbers, we are talking about many tens of thousands of people, not an insignificant number, not an insignificant health problem. Whether or not it has any relationship to herbicide exposure becomes immaterial in that sense, but it is of real veteran concern.

Dr. **ROWLAND OF GEORGIA**. I wonder about the psychological problems that many of the Vietnam veterans are having that we know about. If they had not gone to Vietnam, they may have functioned in society perfectly all right and never had any problems, but the stress that was placed on them by being there and in that situation precipitated problems that they are having now.

Dr. **Gochfeld**. I would be happy to comment. I spent a year in Vietnam in a support capacity as a medical officer. I was not in operations. I saw both Americans and Vietnamese who had suffered stress. I think many people have the tools to cope with stress, some people less successfully than others.

There is no question that there are—I think for many people who have stress related illnesses, there may be a triggering factor but for which they would never have developed their condition.

I am not a psychologist, although I have several psychologists in my division who are working on the Vietnam project. I would not presume to make a more specific interpretation of psychological phenomena.

Dr. **Rowland of Georgia**. That was a question that I asked you, not a statement that I made.

Dr. **Gochfeld**. Okay.

Dr. **Rowland of Georgia**. Mr. Evans?

Mr. **Evans**. Thank you, Mr. Chairman.

I want to thank you for coming before our committee, and I want to thank the State of New Jersey for their Agent Orange Commission, because I think you have provided a great deal of leadership on this issue.

I am not a scientist, either. I guess that is why we have a doctor on our panel chairing the hearing today so we can be equally armed in terms of dealing with some of the scientific evidence that comes before.

What can we generalize, if anything, from incidents like Times Beach, some of the industrial accidents, and even some of the agricultural worker studies? Is there anything we can generalize from those studies that relates to the veterans of Vietnam?

Dr. **Gochfeld**. That is a very far reaching question. Each of those has different lessons. I think from Times Beach, what we are doing in Times Beach or what CDC is doing in Times Beach is studying health effects now after we had a buy-out of that community.

The Times Beach buy-out provided a very clear message in counterpoint to what everyone else in the country was saying that dioxins severe enough that the Federal Government could do something as drastic as buying out a whole city. That was as very profound statement that the Government made, that EPA made.

I think the industrial accidents make it very clear that there are people with acute exposure who develop chloracne. The follow-up on the industrial accidents is not nearly so clear. It is not nearly so good, because some of the worst accidents like the one in 1949 in nitro occurred before people were attuned to long-term epidemiologic follow-up.

The NIOSH study which is looking, among other things, at a cohort of New Jersey herbicide manufacturing workers will address that, because they are including accidentally exposed workers in their midst.

I will say that the original NIOSH proposal did not include blood tests, and it was not a threat but basically a statement that the New Jersey Commission would do the blood tests on the NIOSH cohorts if NIOSH didn't which encouraged NIOSH to approach CDC to do the blood tests, but we basically had made a commitment that we would provide that if the NIOSH study didn't, and I am excited to see that they bought that idea, and I think that will be a very worthwhile study.

The agricultural studies are very interesting but, again, complicated, because they are not looking at Agent Orange. They are not looking at dioxin. They are looking at a variety of herbicides, not just phenoxy herbicides.

I think that in any epidemiologic undertaking—and I speak as an occupational health physician, not specifically as an epidemiologist—you look for concordance among studies. What you pointed out earlier was we keep seeing non-Hodgkin's lymphoma emerging. We see it emerging in the study of agricultural workers exposed to 2,4-D. We see it emerging in a group of Marines. We see it emerging in the CDC cohort.

As you get concordance, you begin to get confidence that there is something there or lose confidence that there is something not there. In fact, concordance is really the most powerful tool we have in dealing with epidemiology.

The clear evidence regarding health effects and TCDD really doesn't emerge from these studies. They weren't designed for that, and we don't know how much people were actually exposed to or whether they were exposed.

So, I think they are important to look at because they point us in directions. I don't think they answer in either way the question of veterans and TCDD.

Mr. Evans. If I am understanding you correctly, to really scientific way to look at this, we need to look at the actual exposure, and I guess to do that, we would have to look at spraying patterns in Vietnam, then the unit records of which individuals being studied—what they reflect, and then, I suppose, even the individual personnel records, because it is conceivable a person on R&R or perhaps in sick bay on a given day might not have been in the area in which Agent Orange was sprayed.

Given that complexity, is it reasonable that we could—and knowing sometimes the inaccuracy of some of these records—come up with a reasonable sample or whatever is needed?

Dr. Gochfeld. The answer is probably yes and no. There are military records. Having traveled around Vietnam on orders, I know how casual some of the military records—or the military records are, by and large, good enough to idnetify groups of people with exposure.

You have heard a discussion of criticism. I prefer to think of it as an exchange of methodological approaches. The New Jersey methodological approach was more focused on identifying groups of individuals from which we would draw, presumably, exposed people rather than trying to ascertain whether John Jones was an exposed person. So, I think that the use of military records as a screen, supplemented by blood tests to identify whether or not a person has a high level, will be a valuable means.

Now, Steven and Jeanne Stellman published a paper in which they used even a somewhat different approach to using military records to come up with an exposure index. So, I don't like the nihilistic viewpoint that it can't be done. I think it can't be done simply, and it probably has to use multiple confirmatory data.

When we did our selection, for example, after we had assigned our people to groups, we submitted each of these records to the environmental support group of DOD and, in each case, they were able to confirm exposed and non-exposed status. So, we felt very good that our approach which was a much more personal subjective evaluation of where people had been was valid, but I wouldn't rely on that alone.

Mr. EVANS. If I could ask one more question, I will be quick.

The DAV recommends in its testimony an archives of frozen blood samples. Do you think that has some merit?

Dr. GOCHFELD. We have actually advocated an archival system. I think, yes, it has merit.

It has proven invaluable in other studies. We are studying the history of AIDS, for example. We discovered also that Legionaire's Disease was not a new event in Philadelphia but, in fact, had been in the population for a long time. We studied that by looking at archived blood specimens that were on hand in various places.

We have proposed an archival system for human tissues—I have mentioned that in the testimony—where if there is a question about exposure and we don't have a clear hypothesis at the moment, when we get information in the future, one can go back, pull the tissues or blood samples from the freezer, and analyze them with up to date, state of the art methods and come up with an answer.

The importance of this may go beyond TCDD. We may discover, as has been alluded to earlier, that that is a red herring or an orange herring and, in fact, it is some other constituent or a medication or 2,4-D itself, and now we want to go back and look for those, and you can't recover. When we are talking about 20-year long studies, we really need the archives. I think that would be valuable.

Mr. EVANS. Thank you, Doctor, for your testimony today.

Dr. ROWLAND OF GEORGIA. Thank you very much for being here. We do appreciate it.

Dr. GOCHFELD. Thank you for the opportunity.

Dr. ROWLAND OF GEORGIA. The next witness is Dr. Michael Gough, Chairman of the Advisory Committee on the Health-Related Effects of Herbicides from the Veterans' Administration.

Dr. Gough, we appreciate your appearing here, and you may proceed in your own manner, if you will.

Dr. GOUGH. Mr. Chairman, with your permission, I will summarize my written statement and ask that the entire statement be included in the record.

Dr. ROWLAND OF GEORGIA. Without objection.

STATEMENT OF MICHAEL GOUGH, CHAIRMAN, ADVISORY COMMITTEE ON THE HEALTH-RELATED EFFECTS OF HERBICIDES, VETERANS' ADMINISTRATION

Dr. GOUGH. Good morning, Mr. Chairman and members of the committee. I am here today as Chairman of the Veterans' Administration's Advisory Committee on the Health-Related Effects of Herbicides.

Until my appointment as chairman of that committee in December, I was not closely involved with its work, and I will limit my remarks to the period of my involvement.

The committee's composition, membership, and its objectives are included in my written statement, and in the interests of time, I will not restate those now.

I will briefly summarize the highlights of our April 15 meeting, the first meeting that I chaired, and when the committee's review of our draft minutes is complete, I will be happy to provide a copy of the complete minutes to the subcommittee.

The committee heard a number of reports about Federal and State programs as well as veterans' service organizations' activities, and time was set aside before the conclusion of the meeting for questions and comments from the audience. We took three direct actions. Two recommendations will be sent to the Administrator, and VA staff agreed to make an amendment to the VA disability compensation manual. I will discuss that amendment first.

The VA Compensation and Pension Service agreed to amend that manual to require that VA employees notify claimants to submit a copy of their Agent Orange examination or to identify the VA medical facility where an examination was done so the VA adjudicator could see it. We did that because there was concern that when veterans called in with claims, they didn't always make it clear that they associated their problem with Agent Orange, and we wanted to be sure there was a possibility of drawing that connection if one existed.

The committee voted unanimously to make two formal recommendations to the Administrator. The committee was troubled by the sporadic publication of the VA's publication, "Agent Orange Review," which was most recently released in February of 1985 and March of 1986. The committee recommended that the agency move expeditiously to publish and disseminate the review.

The advisory committee also expressed dismay about a possible reduction of Federal benefits to Vietnam veterans who receive funds from the settlement of the class action Agent Orange lawsuit. The committee recommended that the Administrator recommend to Congress that benefits accrued from the Agent Orange litigation settlement not be counted against individuals' Federal benefits for services.

Before I close, I would like to make a few comments about the relationship between another VA advisory committee, the Veterans' Administration's Advisory Committee on Environmental Hazards, and the committee on which I sit. The other committee reviews the scientific literature about possible health effects from, one, herbicide exposure and, two, radiation exposure at atomic bomb tests.

While the scope and functions of the two advisory groups are different, clearly, there are some common interests. The Administrator of the Veterans' Administration recently took the advice of our committee and appointed one of its members to serve on both committees.

Mr. Charles F. Conroy, Jr. of the West Virginia Department of Health now serves jointly on the two committees. His report at our April meeting demonstrated that he will be an effective liaison between the two groups.

We have taken one additional step to facilitate and enhance relationships between the tow advisory committees. Our next meeting is scheduled that day before the meeting of the other advisory committee in November to facilitate interaction and communication between the members of the committees and to assist those members and others who wish to attend both committee meetings.

Mr. Chairman, that concludes my oral remarks. I will be pleased to respond to your questions.

[The prepared statement of Dr. Gough appears on p. 187.]

Dr. ROWLAND OF GEORGIA. We have some questions that we will want to submit for you to answer, but I have a couple that I would like to ask you here.

To your knowledge, is there a purpose to be served by obtaining a scientifically top drawer review of the literature related to health effects of Agent Orange?

Dr. GOUGH. Yes, I think there is. I tried to do that in a book that I wrote three years ago, and I think I did a reasonable job with the information that was available then.

However, a great deal has happened in the last three years, and I think it is only by looking at all of the studies and looking for, as the last witness said, concordance or the lack of concordance that we can draw general trends out of this literature, big, complicated, and bulky literature.

Dr. ROWLAND OF GEORGIA. It would be sort of good to get everything together and look at it.

Dr. GOUGH. Yes, sir.

Dr. ROWLAND OF GEORGIA. Let me ask you one other question. A considerable amount of research has been completed or is in the process concerning health effects of herbicides. Most recently is the application of the blood test for dioxin for the Ranch Hand study population. Is there a type of study or another way of conducting a study that has been overlooked in investigating the link between Agent Orange and possible health effects?

Dr. GOUGH. Not to my knowledge.

When I worked at the Office of Technology Assessment, I sat on the Agent Orange Executive Working Group, and we talked often about other possible approaches to those studies, and nothing emerged.

I think the report of the New Jersey Agent Orange Commission emphasizes the importance of the blood test in determining who was exposed. I don't know of any other.

Dr. ROWLAND OF GEORGIA. I guess you have to know whether or not the toxin is present in the body before you can proceed to make a judgment about the health effects.

Dr. GOUGH. About the association. I think, in this case, since the dioxin persists in the body for such a long time, that one would expect there to be some correlation between body levels in a population of people and the presence or absence of health effects.

Dr. ROWLAND OF GEORGIA. Thank you very much for being here today. We certainly do appreciate it.

The next witness is Ms. Helen Gelband who is Project Director, Vietnam Veterans' Issues, Office of Technology Assessment.

Ms. Gelband, thank you very much for joining us today, and you may proceed in your own manner. Your entire statement will be made a part of the record, without objection.

Ms. GELBAND. Thank you.

STATEMENT OF HELLEN GELBAND, PROJECT DIRECTOR, VIETNAM VETERANS' ISSUES, OFFICE OF TECHNOLOGY ASSESSMENT

Ms. GELBAND. One of the advantages of testifying later is that I spent the morning crossing out big parts of my testimony, so I will just try to touch on the areas that other people haven't mentioned, that might be important to the committee.

First, I will just talk a little bit about what we know about exposures of Vietnam veterans to Agent Orange.

When the idea of an Agent Orange study originated, it was always assumed that military records could be used in some way to identify an exposed population. After several years of intensive research in the records, mainly by the Environmental Support Group, of troop movements and activities of military troops, and of herbicide spraying, it became apparent that it wasn't going to be that simple.

The best evidence from the records suggested that exposure was not ubiquitous as had been assumed earlier, but that smaller, discrete groups of men probably were exposed—the Ranch Hands, chemical corpsmen, and others who sprayed base perimeters, sprayed herbicides from boats onto riverbanks, and probably some bystanders who did have incidental exposures but who couldn't be identified through records.

CDC's validation study confirmed what the records suggested: that for most veterans, even those who had served in heavily sprayed areas, there were no significant differences in body burdens of dioxin between the veterans who were in Vietnam and those who served elsewhere. In both groups, the levels for most people were generally within the background range, which we have heard about several times today.

In contrast, those with known exposure, the Ranch Hands, did have elevated levels, suggesting that if there really had been exposure, you could separate people out into groups.

It was this body of information on exposure of ground troops to Agent Orange—the low levels expected from the records and confirmed in the validation study, plus the inability to distinguish exposed from non-exposed based on military records that caused CDC to recommend cancellation of the proposed Agent Orange study. The Agent Orange Working Group and OTA agreed that the study was not feasible as planned and that if further studies of Agent Orange exposed men were to be done, they would have to take quite a different tack.

That is really all I have to say about exposure. I was going to review evidence from some of the recent studies, but that has been done fairly extensively already except for a couple of observations on the VA proportionate mortality study.

I wanted to mention that, consistent with the CDC studies, a very striking finding in the VA proportionate mortality study as an excess of deaths from external causes—motor vehicle accidents; accidental poisonings, which include drug overdoses; and other accidents and injuries. In fact, those findings were more substantial and stronger than the findings that have received much more attention, which are the excess deaths from lung cancer and non-Hodgkin's lymphoma among the Marines. The latter findings were based on much smaller numbers and, in fact, are not consistent with the findings in the Army, while the excess deaths due to external causes were consistent for all veterans.

One comment on the lung cancers finding: to my knowledge, this study is the only one suggesting a link between lung cancer and herbicide exposure. It seems unlikely, given what we know about the other causes of lung cancer, mainly cigarette smoking, that this new finding would emerge from this type of study.

We do urge that if the lung cancer finding is to be followed up that it be done by finding out about smoking prevalence among Marines, both those who were in Vietnam and those who were not in Vietnam. Just finding out about the smoking histories of those who died wouldn't answer that question, but there may be other ways of answering it.

As an example of how smoking rates can differ unexpectedly, in the Ranch Hand study, there was a significantly higher rate of current smoking in the Ranch Handers than in the comparisons, and all of those men served in Vietnam. So, there can be smoking differences that could in fact result in differential rates of lung cancer.

That is all I have for my prepared statement.

[The prepared statement of Ms. Gelband appears on p. 195.]

Dr. ROWLAND OF GEORGIA. I have a couple of questions, and I will try to get them in before we have to go vote. We could count on a vote on the Journal today without a doubt.

You heard the CDC explain its intent and rationale for breaking out as a separate study the non-Hodgkin's lymphoma portion of the selected cancer study. What is your view on the risk of this action with regard to scientific credibility?

Ms. GELBAND. Well, I am not exactly sure what they plan to do. Since OTA recommended looking at that study earlier, I should explain what we envision.

According to the protocol for that study, CDC expected to have about 1,000 cases of non-Hodgkin's lymphoma accrued by the end of 1988, when they were going to stop collecting data for the study. Of the five cancers in the study, there were many more non-Hodgkin's lymphomas than any other type of cancer, and the power—which gives you an idea of what level of risk the study can be expected to detect—for the non-Hodgkin's lymphoma portion of the study was much higher than for any of the other cancers.

It appeared that the length of time planned the recieving subjects into the study was based more on the cancers that would be less frequent. CDC's original estimates suggested that there would be about 800 non-Hodgkin's lymphomas by the end of the third of four years, which would be a very large study in itself.

Our recommendation was that they stop accruing people now but continue to verify the records on those that they had accrued and cut it off earlier than had been anticipated. According to their original protocol, this would not result in any significant loss of power.

Until we know how many they have accrued and what they are planning on doing, I can't comment on whether it might be risky or not. Based on their original plan, it didn't look like there would be any risk to the study.

Dr. **ROWLAND OF GEORGIA**. One other additional question right now. Will the use of the blood dioxin test in conjunction with Ranch Hand health information put to rest the criticism of the Ranch Hand study results as inapplicable to ground troops?

Ms. **GELBAND**. I think knowing that the Ranch Hands have higher levels and having those levels explicitly part of the analysis will make it difficult to argue that somehow the ground troops were actually more exposed. So, yes, I think it will help put to rest that argument.

Dr. **ROWLAND OF GEORGIA**. Thank you very much for being here this morning. We do appreciate it, and there will be some questions that will be submitted to you.

Ms. **GELBAND**. Thank you.

Dr. **ROWLAND OF GEORGIA**. I am going to go vote on the Journal. I will come right back, and we can finish up with this hearing.

[Recess taken.]

Dr. **ROWLAND OF GEORGIA**. I want to call now Mr. John Sommer, Director of Veterans' Affairs and Rehabilitation with The American Legion. He is accompanied by Mr. Samuel J. Walsh, Assistant Director, National Legislative Commission.

Also, I will ask Mr. David W. Gorman who is the Assistant National Legislative Director for Medical Affairs of the Disabled American Veterans to come to the table at this time, too.

Mr. **WILKERSON**. Mr. Chairman, my name is Phil Wilkerson, and I am with The American Legion. Mr. Sommer who prepared the testimony, unfortunately, was unable to be here this morning, and he asked me to appear in his place.

Dr. **ROWLAND OF GEORGIA**. You may proceed in your own manner, and then we will go to Mr. Gorman.

STATEMENT OF PHILIP R. WILKERSON, ASSISTANT DIRECTOR, NATIONAL VETERANS' AFFAIRS AND REHABILITATION COMMISSION, THE AMERICAN LEGION; ACCOMPANIED BY SAMUEL J. WALSH, ASSISTANT DIRECTOR, NATIONAL LEGISLATIVE COMMISSION

Mr. **WILKERSON**. Thank you.

I might also say that if we are unable to provide a response to any questions that you might have for us, we would certainly be glad to provide these in writing with respect to our testimony.

The American Legion takes this opportunity to thank the chairman for scheduling this timely hearing to reexamine the issue of Agent Orange. Many things have transpired on this important issue, yet little progress has been made in determining the health effects of Agent Orange exposure on Vietnam veterans or at least those which the Government will recognize and accept.

Before proceeding with our summary, however, we realize that the purpose of this hearing this morning is oversight and not to consider legislative initiatives, but we wish to express our support for H.R. 4479 which would exclude payments made to veterans and their survivors under the Agent Orange liability settlement fund from being counted as income for pension purposes or eligibility for VA medical care. We would recommend this exclusion from income provision be extended beyond VA programs to include any needs based Government assistance program.

Mr. Chairman, the American Legion is deeply troubled by CDC's conclusion that the agency cannot find enough Vietnam veterans who were exposed to Agent Orange to do a scientifically valid study of its possible effects. A series of major administrative and methodological problems have occurred which have forced the study to a standstill. When CDC conducted a pilot study of its own design, it was no great surprise to us that they then concluded that a study could not then be carried out.

We voiced our concern about the composition of the study population almost two years ago. Thousands of veterans were eliminated from the study population based on criteria set down by CDC, many of whom, no doubt, were heavily exposed to Agent Orange. In fact, it is reported that 83 percent of the original study subjects were disqualified or eliminated based on that revised criteria.

In Vietnam, the United States sprayed more than 12 million gallons of Agent Orange over a country smaller in area than the State of New Jersey. Therefore, we feel it is absurd for CDC officials to now state they cannot find enough people to study. It is unfortunate that CDC was permitted to develop a study that was destined to fail.

The American Legion is mandated to take any and all steps necessary to ensure the Congressional mandate of Public Law 96-151 and subsequent legislation for a study of Agent Orange and related health issues is followed and such studies be completed as expediously as possible. To that end, we urge the assistance of the subcommittee and the full committee in ensuring that the Federal Government fulfills its responsibility to Vietnam veterans and their families in providing answers to the agonizing questions relating to the health effects of exposure to Agent Orange.

Mr. Chairman, that concludes our statement.

[The prepared testimony of Mr. Wilkerson appears on p. 206.]

Dr. ROWLAND OF GEORGIA. Mr. Gorman, we will hear from you now, and you may proceed as you so desire.

STATEMENT OF DAVID W. GORMAN, ASSISTANT NATIONAL LEGISLATIVE DIRECTOR FOR MEDICAL AFFAIRS, DISABLED AMERICAN VETERANS

Mr. GORMAN. Thank you very much, Mr. Chairman.

I want you to know how much we appreciate and welcome the opportunity to be here this morning and to share our thoughts on the various research efforts that have taken place over the years concerning the health status of Vietnam veterans, especially relating to their exposure to Agent Orange.

As you are well aware, Mr. Chairman, numerous research efforts have been initiated over the years concerning exposure to dioxin, the contaminant found in Agent Orange, and what, if any, adverse health effects may result from such exposure. I believe we have heard a wealth of information in testimony this morning as to the findings of that research to date.

Much of this research has been completed and analyzed. Much more is ongoing, some of which will be completed in the near future and some which will not be completed for many years to come.

The fact is that all of these research endeavors are, in our view, clouded with certain uncertainties and fraught with differing and conflicting interpretations of the scientific data. To further complicate this complex and frustrating issue is the belief held by many people that the scientific and medical communities will not be in a firm position to provide answers to the many questions surrounding the issue of what, if any, adverse health effects result from exposure to Agent Orange.

Given the fact that it has been over 20 years since the initial spraying of Agent Orange occurred, and recognizing that thousands of veterans and their families are fearful, confused, frustrated, and uninformed while waiting for science to provide answers, we believe it is now time to take some positive action regarding this issue.

Mr. Chairman, our written testimony outlines five specific recommendations which we believe to be reasonable, feasible to do, and warranted, and we would ask the subcommittee to consider them carefully.

Mr. Chairman, last month, the Centers for Disease Control released the Vietnam Experience study and published it in the Journal of the American Medical Association. The study was designed to evaluate possible health effects of the general Vietnam experience.

To conduct this study, two groups of veterans were studied. One group consisted of veterans who served in Vietnam. The other group comprised veterans who served during the same period but not in Vietnam. For all practical purposes, the two groups were similar in all other respects.

Over 15,000 veterans were interviewed via telephone, and nearly 4,500 veterans underwent comprehensive medical and psychological interviews.

The most noteworthy differences detected on the medical exams showed Vietnam veterans were afflicted with a significantly greater degree of hearing loss, occult blood in the stool, past infection of hepatitis B, and lower sperm concentrations and sperm cells than were non-Vietnam veterans.

The psychological aspect of the study showed a more prevalent incidence of anxiety, depression, and alcohol abuse among Vietnam veterans. Also, it was found that approximately 15 percent of Vietnam veterans met the established diagnostic criteria for post-traumatic stress disorder.

Finally, it was determined that reproductive outcomes and the health of veterans' children were similar between the two groups.

In our view, Mr. Chairman, the overall results of the Vietnam Experience study should be interpreted as good news for Vietnam veterans, except perhaps for the psychological component of the study. We wait anxiously for the results of the national post-traumatic stress disorder survey that is being conducted by the Research Triangle Institute. Hopefully, that will shed some additional light and insight into the post-traumatic stress disorder issue.

That concludes my oral remarks, Mr. Chairman. Thank you.

[The prepared statement of Mr. Gorman appears on p. 217.]

Dr. ROWLAND OF GEORGIA. It seems there is pretty much agreement that there has been some significant psychological problems that have been caused by the war in Vietnam and what took place there. The principal problem seems to arise with physical problems that Vietnam veterans seem to be having and scientifically being able to tie that down. We have heard testimony from various groups over a period of time about this.

Mr. Wilkerson, let me ask you, you said—well, most of your testimony was devoted to technical criticism of the CDC and their work. The CDC has been extensively reviewed by many experts. I wonder if you could give us the names of people that your organization has consulted with, experts there, who disagree so that we might contact them and get information from them, too.

Mr. WILKERSON. Yes, Mr. Chairman.

The American Legion is working with the Stellmans, Jean and Steven, who are epidemiologists associated with Columbia University. They have also been assisting us in a Columbia University and American Legion study of Vietnam veterans. That was a study that was developed. It was a scientifically established study of members of our organization, those veterans who served in Vietnam as well as Vietnam-era veterans.

So, they were consulted with regard to the findings of this most recent CDC study, and their analysis provided the basis for the latter part of our testimony.

Dr. ROWLAND OF GEORGIA. I appreciate those names and any additional ones that you might have.

As was pointed out earlier and discussed earlier, there may be genetic differences in individuals that can make a difference also, and we are just beginning to get into that area. There are certainly variables that make a scientific study difficult to do so far as the physical problems that might have been caused by exposure to Agent Orange.

Mr. Gorman, let me ask you, your idea of a tissue archive was supported by several witnesses this morning. Have you looked into the cost of such an archive? Do you have any idea about that?

Mr. GORMAN. We haven't looked into the actual cost of setting it up, because, basically, it is a concept that we have while not being really familiar with all the intricacies that might go into it. However, I think the initial figure we have is $100,000 to set up the basic archiving and a minimal amount of money in the following years simply to staff and maintain it. So, it would be a minimal cost, to our knowledge.

Dr. ROWLAND OF GEORGIA. Thank you.

Counsel for the minority.

Mr. WILSON. Mr. Wilkerson, you partially answered a question I was going to ask. What is the status of the study that the American Legion commissioned at Columbia University?

Mr. WILKERSON. The last part has undergone peer review. The Stellmans have contracted with a medical publication and are making arrangements for publication at an early date.

Mr. WILSON. Do you have any idea when it is going to be released?

Mr. WILKERSON. No, sir, I don't.

Mr. WILSON. When it is released, could you furnish it to the committee?

Mr. WILKERSON. Absolutely.

Mr. WILSON. Thank you.

Thank you, Mr. Chairman.

Dr. ROWLAND OF GEORGIA. I don't have any additional questions, and I wanted to express my appreciation to you for being here this morning.

Mr. WILKERSON. Thank you, Mr. Chairman.

Dr. ROWLAND OF GEORGIA. We may submit questions to you.

For the last panel, I will ask Mr. John Bollinger who is Associate Legislative Director for PVA; Mr. Gordon Thorson, Special Assistant for the National Legislative Service, Veterans of Foreign Wars; and Mrs. Mary Stout who is President of the Vietnam Veterans of America who is accompanied by Mr. Paul Egan to please come forward.

I want to express my appreciation to all of you for being here this morning. Mr. Bollinger, we will ask you first if you will proceed.

STATEMENT OF JOHN BOLLINGER, ASSOCIATE LEGISLATIVE DIRECTOR, PARALYZED VETERANS OF AMERICA

Mr. BOLLINGER. Thank you very much, Mr. Chairman.

It is a pleasure to be here today, and I thank you for inviting Paralyzed Veterans of America.

The search for clues to discover any potentially adverse health effects of exposure to Agent Orange has been long and very difficult, as we all know. At times, the science hasn't been perfect, and many times, the full commitment to pursue that science hasn't been complete, but we feel we are still much farther down that road than we were ten years ago.

Vietnam veterans and their families now have far more answers as to their overall health status than they did before. Still, as this investigation is pursued, we might never find the proper combination of clues which could establish a concrete link between exposure to Agent Orange and certain diseases, but that shouldn't stop us from supporting any effort to do so.

Today, I would like to comment on the results of two major studies. Last fall, the VA released the findings of its study on mortality. In our written testimony, we have reviewed the study in depth, but here are a few major findings that I would like to discuss today.

As a group, there appears to be no remarkable difference in the major causes of death between the men who served in Vietnam and veterans who did not serve in Vietnam, with few exceptions.

When all malignancies were grouped, Army and Marine Corps Vietnam veterans did not exhibit an excess of cancer when compared to their counterparts who did not serve in Vietnam.

Although some studies have suggested that individuals exposed to dioxin could be at increased risk of soft-tissue sarcoma, no excess was seen among Vietnam veterans in this study.

From an epidemiological standpoint, taking both Army and Marine Corps Vietnam veterans as a group and comparing them with equivalent veterans who did not serve in Vietnam, there appears to be no major difference in the mortality experience of either veteran cohort.

Newly developed scientific techniques which can assay dioxin levels in blood samples taken from Vietnam veterans today could help to trace clues to exposure 25 years ago, but who is not to say that those trace elements in the veteran's blood were not absorbed or ingested by exposure to this chemical compound which has been in commercial use and environmentally pervasive in this country, not just Vietnam, for decades. From the testimony I have heard today, though, I think that with extensive background and identifiable study groups, perhaps blood tests would be a positive avenue to go.

Vietnam veterans in a combat situation over a period of months or years in a tropical environment were exposed to a multitude of potentially harmful experiences and agents which can carry with them adverse long-term effects. Exposure to a tropical environment brings contact with a host of organisms and parasites, not to mention the insecticides, chemicals, and drugs aimed at combatting those agents to keep troops fighting in the field. In general, no matter where it is, war is just not a very healthy place.

Last month, the CDC released the findings of the Vietnam Experience study. Very briefly, the findings revealed certain psychological problems were significantly more prevalent among Vietnam veterans than among non-Vietnam veterans. Vietnam veterans reported current and past health problems more frequently than did non-Vietnam veterans. However, the results of the medical examinations showed few current objective differences in physical health between the two groups.

PVA believes the results of this study should be encouraging for the vast majority of Vietnam veterans. The study revealed no insidious undercurrent of disabilities undermining the physical health and well-being of the Vietnam veteran population. In fact, the study showed clearly the opposite: the vast majority of Vietnam veterans have readjusted from military service not only socially and economically but from a standpoint of general physical health at a level equivalent to their non-Vietnam veteran peers.

One of the most disturbing revelations of the VES study was the demonstrated incidence among Vietnam veterans of a potential anxiety reaction over Agent Orange itself. For many Vietnam veterans, the fear of Agent Orange can actually be worse than Agent Orange itself. Hopefully, this study, with its positive impliations for the health and well-being of the vast majority of Vietnam veterans, can help allay those fears.

That concludes my comments.

[The prepared statement of Mr. Bollinger appears on p. 225.]

Dr. Rowland of Georgia. Thank you, Mr. Bollinger.

Mr. Thorson?

STATEMENT OF GORDON THORSON, SPECIAL ASSISTANT, NATIONAL LEGISLATIVE SERVICE, VETERANS OF FOREIGN WARS

Mr. Thorson. Mr. Chairman, Veterans of Foreign Wars is privileged to have the opportunity to present its viewpoint to this subcommittee. We appear today to present written and oral testimony in an effort to find a final resolution to the Agent Orange issue.

The scientific and medical community has already spent ten years researching and studying the effects of dioxin exposure. They only conclude that more time is necessary to study the issue and develop or produce complete scientifically valid evidence, thus establishing without a doubt the residual effect of Agent Orange on veterans exposed to its deadly toxin, dioxin 2,3,7,8-TCDD.

While the experts are attempting to achieve scientific certainty, exposed veterans are left to question the results of their studies and try to determine how the results related to their individual disabilities and concerns. The veteran and medical community has focused on a problem thought to be of epidemic proportions. While most everyone has searched for evidence of a widespread problem, little has been done to address the current needs of individual veterans.

Legislation must be developed that would provide a reasonable method of establishing a valid claim for VA compensation benefits.

The VFW concludes that continued research and study of Agent Orange related disabilities is needed and necessary to ensure complete knowledge of related residual disabilties and allow complete understanding of the effect dioxin has had on the human system. However, we firmly believe, as outlined in our written testimony, that the scientific community should be required to establish an initial list of disabilities logically associated with dioxin exposure. At the same time, they should set the level of dioxin considered unacceptable.

This action would allow the start of a logical process toward a final resolution. Any in-country Vietnam veteran claiming residual disability as a result of Agent Orange exposure could then be given a blood serum test or an adipose tissue test, and if, one, the blood serum or adipose tissue test demonstrates an abnormal level of dioxin and, two, the veteran's military record shows in-country service in Vietnam and, three, the veteran has a residual presumptive disabilty that can be attributed to retained dioxin, then it would be reasonable to award service-connected disability beneifts.

We call for and will support legislation designed to give fair, compassionate, and deserving treatment to veterans found suffering from the residual effects of dioxin exposure.

Thank you, sir.

[The prepared statement of Mr. Thorson appears on p. 230.]

Dr. Rowland of Georgia. Thank you, Mr. Thorson.

Mrs. Stout?

STATEMENT OF MARY STOUT, PRESIDENT, VIETNAM VETERANS OF AMERICA; ACCOMPANIED BY PAUL EGAN, LEGISLATIVE DIRECTOR

Mrs. Stout. Thank you, Mr. Chairman.

I certainly appreciate the opportunity to address you today, particularly because I know of your strong leadership on the issue of presumptive compensation as evidenced by your support for veterans with illnesses associated with radiation exposure in our fellow veterans has given us new hope on the issue of compensation for Agent Orange and related disorders can be overcome through Congressional action.

I cannot go on without commenting on Mr. Harvey's statement this morning, because I feel as a Vietnam veteran that I was insulted by his attributes to Vietnam veterans who are concerned about this issue as being a matter of guilt, that it is symbolic of war.

The veterans I have talked to whose skin is falling off their hands are not dealing with guilt. The doctor, the battalion surgeon who was the president of our chapter and died last year from liver cancer that he felt sure was caused by Agent Orange, was not dealing with guilt.

Yesterday, I got another letter. A chapter president died from an illness associated with Agent Orange exposure. These people aren't dealing with guilt. They are dealing with illness. They are dealing with questions that are unanswered. They are dealing with families with nowhere to go and no compensation.

I am here today to seek your consideration of passage of H.R. 3486. We support this legislation because we believe it is an appropriate, even though a very modest attempt to begin to address the issue of Agent Orange exposure in Vietnam.

The proportionate mortality study of the Veterans' Administration certainly made the link with non-Hodgkin's lymphoma and lung cancer, and our written statement has a lengthy explanation of that. It also mandates that the Veterans' Administration contract, with an unbiased, non-governmental scientific entity to review all the relevant and ongoing studies to determine other illnesses that should be compensable under the presumption of increased risk from exposure to Agent Orange.

One aspect of H.R. 3486 which may not be as clear to this committee as, certainly, non-Hodgkin's lymphoma and lung cancer is immunosuppressive aspects of dioxin. Attached to our statement today is the statement of Dr. Thomas Gasiewicz who is associate professor of toxicology at Rochester University. I think his information will be very helpful for the committee's looking at the immunosuppressive aspects.

The final issue in H.R. 3486 which we also support requires that the Veterans' Administration evaluate the data that has been collected on those veterans who have come to the Veterans' Administration for illnesses associated with Agent Orange exposure.

I have to tell you quite honestly, Mr. Chairman, that while we would love to see that happen, we heard the figure today of 1.1 million visits of Agent Orange veterans who say they have illnesses associated with Agent Orange. I believe that the 1.1 million is a publicity stunt by the Veterans' Administration.

We received information last year, and we were quite shocked when we got that information of 1.1 million visits. When we asked Dr. Barkley Shepherd who was then head of the VA Agent Orange program, what is wrong with these veterans, he told us that the VA was not keeping track of the illnesses.

Over the course of several months, we talked to a number of veterans in our organization and found out that those who are going in for their regular PTSD evaluation or visit, if they were going in for help with their prosthesis, if somewhere along the line they had marked on a VA form that they were a Vietnam veteran and felt they were exposed to Agent Orange, they were being counted as an Agent Orange visit.

I think this is something that is unconscionable—to have a medical organization like the Veterans' Administration completely disregard the importance of the concerns of veterans about Agent Orange and to use inflated figures as a publicity stunt and to keep no records of the concerns of veterans as to what they are coming for.

In conclusion, I am sure I don't need to remind this committee that you have already passed in Congress three pieces of legislation to address the Agent Orange issue. The first mandated the study that has never been done.

The second called for health care for Vietnam veterans with illnesses they associated with Agent Orange. I have already explained the problem with even figuring out what health care they have gotten and what illnesses they have gone to the VA for.

And the third called for compensation. We know that no compensation has been given to any Vietnam veteran for illnesses associated with Agent Orange.

I would like to ask your permission for one more moment for Paul Egan, our legislative director, to add one piece of information I think is very important to this committee.

Thank you.

Mr. EGAN. Thank you, Mr Chairman.

There seems to be a great deal of unanimity among the Government's witnesses this morning in holding that there are no problems arising from Agent Orange, there is no scientific evidence to support a relationship between exposure and disease, that we can trust the Veterans' Administration, that we can rely on the Veterans' Administration to come forward and ask for compensation when that is justified. We heard that from Mr. Harvey.

From Mr. Don Newman, we heard that there is cause and effect relationship between Agent Orange and disease. We also heard that there is no increase in dioxin blood levels in ground troops versus others.

Perhaps it is not surprising that there is unanimity among Government witnesses since the head, Don Newman, of the Agent Orange Working Group in the White House sent out a memo dated April 1, which ironically was shortly after the Ranch Hand update was submitted by Dr. Albanese in which several problems with the

Ranch Hand study were found. If I can read from this, in part it says:

"The release of any report without the review mandated by the Agent Orange Working Group procedure could constitute a serious breach and many undercut our credibility. Any premature release could cause embarrassment to the Government."

Well, are we concerned about whether the Government is embarrassed about the truth or are we concened that the truth come to the fore? I don't know whether the politicians over at the White House are better equipped than the scientists to determine what ought to and what ought not to come out, but while this particular memo may or may not mean something, I would like it to be added to the record just for the purpose of making clear that there is a pretty good possibility that the Government isn't being completely candid about what the science does indeed say and what it doesn't say.

So, with your permission, I would like to have that entered into the record.

Dr. ROWLAND OF GEORGIA. Without objection, it will be made part of the record.

Mr. EGAN. Thank you.

[The prepared statement of Mrs. Stout appears on p. 238.]

[The memorandum appears on p. 275.]

Dr. ROWLAND OF GEORGIA. Mrs. Stout, let me ask you something. You mentioned the 1.1 million visits that had been made by Vietnam veterans, many for PTSD prosthetics. Do you have any idea how many were made for other problems, diseases?

Mrs. STOUT. I have no idea, Mr. Chairman, because the Veterans' Administration, as I said, has not broken out what the illnesses are.

Our understanding of the legislation—and we agreed with that—was that when a Vietnam veteran came in and said "I have an illness that I believe is associated with my exposure to Agent Orange in Vietnam" the Veterans' Administration would give them health care. We would expect that the Veterans' Administration would have at least counted what those illnesses are.

It is not their regular visit for their disability. It is not a cold, unless they come in and say it is a cold.

There was talk that some people were sending veterans to the VA saying you can get free health care if you go over there and tell them this is associated with Agent Orange. We certainly did not encourage anyone to do that.

We have no idea, and that is why this legislation and the provisions of it of asking the Veterans' Administration to go through that data and weed out what those illnesses are is very important.

Dr. ROWLAND OF GEORGIA. The question is, if someone comes in with a legitimate complaint referring to exposure to dioxin, a Vietnam veteran, whether or not it would be very practical to do a serum dioxin level on that individual. I don't know that there has ever been done or attempted. It is a very expensive test to do, as you have heard. I don't know whether it is possible to do a qualitative rather than a quantitative test or not, but I think that is something we might consider and ask about.

Mrs. **Stout**. Well, I think one of the considerations about the serum dioxin level—an we had considered that as supporting legislation to include that—is that we then say that you must prove, in fact, that you have an elevated level of dioxin either to receive this service or to receive compensation.

Given the half-life and the differences in metabolism, this may be very difficult. We don't know if illness related to dioxin is caused by a very small amount of dioxin or by a very large amount of dioxin or if a person could have that illness start and then the dioxin be excreted. It is a very difficult thing.

It is helpful for the scientists to be able to look at increased levels and to try to make correlations with who was highly exposed so we can look at that, but to treat veterans or to give compensation based on the dioxin level of their blood to us seems, first of all, unfair and probably impractical in determining what illnesses are.

I want to go back to the thing about the 1.1 million. We did write to the Veterans' Administration and ask about that figure. We got letters back saying that the figure was inflated. In fact, they had gone back and rechecked, and they had lowered the figure to 300,000 and, again this morning, we heard Mr. Harvey come back with the figure of 1.1 million.

So, there is certainly a discrepancy within the Veterans' Administration about how many people they have treated.

Dr. **Rowland of Georgia**. This of course, is an oversight hearing and is not related to compensation, so those who testified here this morning testified from a scientific standpoint about what they had found, and it wasn't based on presumptions and things of that nature. There are some presumptive disabilities, as we well know.

Let me ask just one other question, and I will ask this of all of you. Would your organizations support a major attempt to summarize all the—we have a lot of existing research out there—summarize all of this research and try to bring it together to get some kind of interpretation on it and then try to reach some kind of concordance about just what is going on?

Mr. **Thorson**. Yes. In fact, that is the very essence of the VFW testimony. We think it is important to have the scientific community bring together all available information and come up with some results, something that can be interpreted in a list of disabilities that can be attributed to dioxin.

If we have that, it is a beginning. With that, coupled with the dioxin blood serum test, we should then be able to establish some link, and the Veterans of Foreign Wars believes that this blood test, that has been recently developed, is the link. Once we are able to determine the amount of dioxin in a man's or woman's system, that should be very significant in identifying that person as a victim of Agent Orange.

What is especially important, after listening to the testimony given by the gentleman from New Jersey, his testimony indicated that not only can they identify the level of Agent Orange or dioxin 2,3,7,8-TCDD in a veteran, but they can determine whether or not the dioxin in his system was a residual effect of Agent Orange specifically. They can tell the difference between a farmer who has been exposed to dioxin and a veteran farmer who was in Vietnam who has retained 2,3,7,8-TCDD, and that is very significant, I think.

Mrs. **Stout**. Mr. Chairman, we would support that. However, that is what we thought the Environmental Hazards Committee was about. Obviously, that hasn't been done.

We would certainly support that, but we would want it to be an independent, unbiased agency, and I do not believe that Vietnam Veterans would accept the Veterans' Administration at this point as the organization to do that.

Mr. **Bollinger**. Mr. Chairman, in answer to your question, PVA could support such action.

Dr. **Rowland of Georgia**. Well, let me again thank all of you very much for being here this morning. It has been a long hearing, but I think it has been a good hearing, and maybe we will get some answers out of it.

Does counsel have any questions?

Mr. **Wilson**. No, thank you.

Dr. **Rowland of Georgia**.We stand adjourned.

[Whereupon, at 12:45 p.m., the subcommittee adjourned, to reconvene subject to the call of the Chair.]

APPENDIX

STATEMENT OF SENATOR JOHN KERRY, A U.S. SENATOR FROM THE STATE OF MASSACHUSETTS

House Veterans Affairs Committee
Hearing on Agent Orange
June 8, 1988

Mr. Chairman, thank you for this opportunity to submit a statement to this Committee on the subject of Agent Orange. I appreciate your willingness to hold this hearing and to consider legislation providing compensation for the victims of Agent Orange.

Agent Orange is a pressing concern -- literally a matter of life and death -- for many Vietnam veterans. The issue will not go away. It is time for Congress to address the concerns of Agent Orange victims, and to provide compensation for those who are suffering from diseases caused by exposure to Agent Orange. I hope that you will join me in leading that fight.

We need to avoid making Vietnam veterans the last victims of the Vietnam war. But our debt to Vietnam veterans should not be repaid only in rhetoric. The Welcome Home parades are important. The Vietnam Memorial is important. The parades, the concerts, the resolutions, are all important. But there is something more important than symbolism. And that is justice and fairness towards Vietnam veterans.

We now have a proposal to elevate the Veterans Administration to Cabinet-level status. Make no mistake -- I support that legislation, and I think that the symbolism and the recognition of veterans that it implies is good. But I am concerned that we are once again falling into the trap of substituting symbolism for substance.

Far more important than symbolism is the reality of how we treat our veterans who are still suffering. And I believe that it is nothing less than wrong on the facts to tell Vietnam veterans that we cannot compensate for diseases which were caused by their exposure to Agent Orange in Vietnam. It is offensive to veterans to tell them that there is not enough "scientific evidence" to justify compensation.

Mr. Chairman, as time goes on, the evidence on Agent Orange becomes stronger and stronger. That is not surprising, since we know that it takes many years for cancers and other disease to develop which are linked to Agent Orange exposure. Let me review just a few of the studies which have come out in the past few years on this subject.

In 1983, the VA Agent Orange registry found excessive cancers among Vietnam veterans of two types -- non-Hodgkins lymphomas, and cancers of the oral cavity and pharynx.

A 1983 study by the Massachusetts Agent Orange Commission found excessive numbers of soft-tissue sarcomas and cancer of the kidney among Vietnam veterans exposed to Agent Orange.

The 1984 Ranch Hand baseline study found higher amounts of skin cancers and systemic cancers, twice as many cancers of the lip, oral cavity and pharynx, and three times as many cancers of the respiratory system, chest and genito-urinary system.

A 1985 study in Wisconsin found excessive incidences of soft-tissue sarcomas among Vietnam veterans who had been exposed to Agent Orange.

A 1986 study in West Virginia found higher incidences of non-Hodgkins lymphomas, and cancers of the testes, larynx, and respiratory system among Vietnam veterans.

The preliminary results of the CDC Vietnam Experience Study released in 1987 showed excessive instances of lymphosarcomas, leukemia, and brain cancer among Vietnam veterans.

The VA Mortality Study released in 1987, a survey of 50,000 veterans, showed rates of death due to non-Hodgkins lymphoma 110% higher than normal, and deaths due to lung cancer 58% higher than normal among Marines who served in areas heavily sprayed with Agent Orange.

The 1987 Ranch Hand follow-up study showed excessive incidence of skin cancers, systemic neoplasms, lymphomas, soft-tissue sarcomas, three times as many cancers of the oral cavity and pharynx, twice as many cancers of the bronchus and lung, and three times the number of testicular neoplasms.

And the report released on the Ranch Hand study in March of 1988, at the request of Senator Daschle and myself, showed higher incidences of tumors, birth defects, psychological disorders, blood toxicity, and cardiovascular problems.

In addition, the results which have just been released this week from the CDC Vietnam Experience Study show higher incidence among Vietnam veterans of fertility problems, low sperm count, depression, alcohol problems, anxiety disorders, skin disorders, and birth defects. I hope that these results will be made a part of the record, and studied carefully.

Other studies relating to dioxin have also shown similar results. A 1986 study by the National Cancer Institute of farmers in Kansas who had been exposed to herbicides similar to Agent Orange showed an incidence of non-Hodgkins lymphoma six times higher than normal. Studies in Sweden showed incidences of soft-tissue sarcoma five to seven times higher than normal with phenoxy-herbicide exposure. And other studies have shown similar results.

So to those who say "we don't have enough evidence", I would ask -- How high does the body count have to go? How many more Vietnam veterans have to die before we have "enough evidence" to start admitting the truth and compensating veterans?

Our legislation would establish a presumption of service-connection for two of these diseases, non-Hodgkins lymphoma and lung cancer. In addition it would ask the National Academy of Sciences to review the evidence of the scientific studies and compile a list of other diseases which which are linked to suppression of the immune system, which may be linked to dioxin or Agent Orange exposure. If appropriate, these diseases would be added and a presumption of service-connection created.

Mr. Chairman, it is important to understand how strongly Vietnam veterans feel about this subject. At Vet Centers throughout Massachusetts, and at VA clinics and hospitals, I have met with Vietnam veterans and veterans groups. And I know that Vietnam veterans feel very, very strongly about this issue. You cannot tell a Vietnam veteran that there is "not enough evidence" on Agent Orange. They know what the evidence is. For one thing, the evidence is in their own bodies, and even worse, in the bodies of their children. They have no doubt about that.

Last month, we finally won the fight to provide compensation for victims of atomic radiation. But before we won the fight for atomic veterans, some of them had to wait 40 years or more for compensation. And many of them died before they reached that day.

We should not make Vietnam veterans wait 40 years for compensation. I hope we are not going to wait until the 21st Century to tell Vietnam veterans that the evidence is now strong enough, and we are ready to compensate them.

I know that there is still controversy about the effects of Agent Orange. There may always be controversy, just as there may always be controversy about the Vietnam war itself. But the legislation that I have introduced is an attempt to end the controversy, and put the divisions of the Vietnam war behind us.

I am not saying that the studies should stop. Studies on Agent Orange, on dioxin and on cancers should continue.

But the Ranch Hand study will not be complete until the year 2002. And we cannot ask Vietnam veterans to wait any longer.

The CDC has told us that they cannot complete their study on Agent Orange, because they cannot measure the levels of dioxin in the blood of Vietnam veterans. That is perhaps not surprising, since in many cases 15 or 20 years or more have passed since the exposure to Agent Orange in Vietnam. But that does not mean that there are no lingering health effects, no diseases or damage caused by that exposure. Let us be clear on that point.

Mr. Chairman, Vietnam veterans deserve to be told the truth. I believe that just as important as compensation itself is the simple recognition and admission of the fact that Vietnam veterans and their children are suffering -- from cancers, tumors, birth defects and other conditions linked to Agent Orange. It is time that we admitted that fact as a nation. Vietnam veterans do not want any special dispensation or special treatment. They simply want the same treatment that has been accorded to every other group of veterans under the law. Where there is a medical condition caused by military service, there should be compensation.

Perhaps all of here today will not agree on whether Agent Orange caused all of the diseases I have listed. But the evidence of the Vietnam Experience Study and other studies clearly shows that those diseases are associated with service in Vietnam. And that is really the critical point. If a veteran is suffering today from a disease caused by his service in Vietnam, then he should be compensated. It is that simple. That is the way the system is supposed to work.

Mr. Chairman, I am deeply dismayed by the attitude of this Administration on the issue of Agent Orange. As with so many issues, the rhetoric is out of touch with the reality. They tell us that Vietnam veterans are "national heroes". But they continue to turn a deaf ear to Vietnam veterans who need help.

The VA continues to tell us that only chloracne, a skin disorder, is linked to Agent Orange exposure. Only a handful of veterans have been compensated even for this disease. Meanwhile, the VA itself only reviewed seven out of more than a thousand studies relating to Agent Orange before promulgating its regulations on the subject. And at the same time, they continue to tell us that "more studies are needed".

We know some of the reasons for this stonewalling and foot-dragging. They are afraid of the cost. They say it will cost too much money to compensate Agent Orange victims. They are afraid of legal liability. And they don't want to admit that they were wrong.

We heard all those same arguments in the debate over atomic veterans. And we rejected them. I would only add that the same consideration applies to Vietnam veterans. If Agent Orange veterans deserve compensation, they should be granted compensation.

But let us do it this year. Let us do it now. It has already been over 25 years since the spraying of Agent Orange in Vietnam started in 1962. It is already 13 years since the last American troops left Vietnam. And it is already too late for many Vietnam veterans.

People are suffering. People are dying. That is why we are here. And we cannot be indifferent to that suffering.

Mr. Chairman, many Americans questioned the war in Vietnam. Not all of them supported it. But Vietnam veterans gave their country the benefit of the doubt. In fairness to them, and in memory of those who gave their lives, I hope that we can give them the same benefit of the doubt. I hope that we can find it in ourselves to do as much for them, as they have already done for us.

Thank you.

THOMAS DASCHLE
SOUTH DAKOTA

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STATEMENT OF SENATOR TOM DASCHLE

BEFORE THE HOUSE COMMITTEE ON VETERANS' AFFAIRS

SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

JUNE 8, 1988

Mr. Chairman, thank you for the opportunity to testify today to discuss the continuing problem of Agent Orange and its effects on Vietnam veterans. As you know, Representative Lane Evans, Senator John Kerry, and I have introduced H.R. 3486 and S. 1787, legislation to establish, for disability compensation purposes, a presumption in favor of Vietnam veterans suffering from diseases associated with exposure to Agent Orange and/or Vietnam service. I am confident that my colleagues will find the case for compensation compelling once the full truth is known about current dioxin research and the government's treatment of this issue, which has been, at best, woefully inadequate.

Mr. Chairman, I know that today's hearing is intended to focus primarily on the scientific progress with respect to Agent Orange. I think I can safely say that, within the government -- for whatever reason -- there hasn't been much. One reason is that none of the current studies has had the benefit of an accurate exposure assessment. The lack of such an exposure index leaves the studies open to misclassification, which would have the effect of potentially masking actual dioxin effects.

Virtually every credible scientist has stressed the importance of an accurate exposure index in detecting potential dioxin effects and dose-response relationships. The current studies lack that ability, but that doesn't stop government officials from asserting that there is no cause-and-effect relationship between dioxin -- or even Vietnam service -- and certain diseases. Nor does it stop them from making extremely misleading statements like, "We observed no dose-response relationship to explain this group difference."

As I said earlier, there are encouraging signs at the Air Force, for Air Force scientists are currently paving the way for the first data analysis based on estimates of actual dioxin body burden. They and other scientists, including those at CDC, have characterized the current methods for determining exposure as "guessing games," and they point out that we will have "a whole new study" once the new exposure index is completed. I applaud the Air Force, the various state Agent Orange commissions, and CDC for this breakthrough and look forward to the day when we will reap its benefits.

I suspect another reason we have seen relatively little progress is that this Administration has not been very interested in resolving this issue. The Agent Orange story is a seemingly never-ending saga of delays, neglect, suppressed information, and general bad faith. I have been following this issue closely for almost ten years. While I realize that there are sometimes legitimate reasons for delays -- this problem is, after all, a complex one -- the Administration's strategy appears to be to capitalize on the complexity, draw the issue out as much as possible, and outlast the opposition.

The odds work in the Administration's favor. The science is difficult, and if the studies take long enough, there will be no study subjects left, no one to compensate. Over time, people will grow tired of the issue. It is not a bad strategy, for I can tell you that even I have grown weary of the endless efforts to resolve this issue. I want to resolve it and get on to other things. But I am putting my opponents on notice: I will not give up until I am satisfied that the legitimate needs of veterans have been met.

I think I know what the government witnesses will say today. Many of them were at the May 12 Senate hearing, where, as usual, they appeared to be more interested in backing away from their findings than engaging in objective scientific inquiry. When asked about increased disease rates for Vietnam veterans, they say they are probably statistical flukes, but that they will "watch them." They go on to "reassure" veterans that there is "no cause-and-effect relationship" between Vietnam service and veterans' disabilities. Mr. Chairman, they can't have it both ways. They can't assume the roles of objective scientists at the same time they make premature, but definitive judgments about the subject of their studies.

As I mentioned earlier, the science is strongly suggestive of a connection between Agent Orange and/or Vietnam service and certain disabilities, but not definitive. The goal of definitive evidence is a long way off, and it may not be attainable at all. In the meantime, many veterans wait, and some veterans die. And we must ask ourselves if veterans haven't become innocent victims caught between a lack of scientific progress and a Congress that fails to act.

In conclusion, Mr. Chairman, I want to thank you for conducting this hearing. H.R. 3486 represents an attempt to address the Agent Orange problem in a responsible, comprehensive way. Since most of these witnesses heard my explanation of this legislation in the May 12 Senate hearing, I will not repeat myself. Instead, I am providing a legislative fact sheet for the Committee's review, and I would be happy to answer any questions about it.

I welcome suggestions as to how the bill could be improved. If there are legitimate concerns about specific language in the bill, I am hopeful this hearing will provide an opportunity to consider them. In the process, however, we should not forget that many Vietnam veterans continue to suffer as we debate the most effective, compassionate way to deal with this problem.

VETERANS' AGENT ORANGE DISABILITIES ACT OF 1987: FACT SHEET

The Veterans' Agent Orange Disabilities Act of 1987 sets out congressional findings that there is sufficient scientific evidence to warrant a presumption of service connection for a) non-Hodgkin's lymphoma and lung cancer, and b) disabilities associated with immuno-suppressive effects of exposure to dioxin and other toxic herbicides.

The bill also amends title 38 USC to establish a presumption of service connection for veterans who served in Vietnam, were exposed to dioxin or other toxic herbicides, and are suffering from the following conditions:

1) non-Hodgkin's lymphoma,
2) lung cancer manifested within 25 years of the veteran's last day in Vietnam, and
3) disabilities that are reasonably associated with suppression of the immune system as a result of exposure to dioxin or other toxic herbicides.

The bill adopts the Veterans Administration's definition of exposure to Agent Orange for compensation purposes. The bill acknowledges the VA's regulations that find it reasonable to presume that "any veteran who performed active military, naval, or air service in the Republic of Vietnam during the Vietnam era was exposed to dioxin or other toxic herbicides during such service," and applies that same standard to compensation language.

In order to determine disabilities reasonably associated with supression of the immune system as a result of exposure to dioxin or other toxic herbicides, the bill authorizes the National Academy of Sciences (or another appropriate nonprofit private scientific organization if the National Academy of Sciences declines to participate) to establish a committee to survey existing and ongoing scientific data.

Within a year of enactment, the Academy would submit a report listing the disabilities associated with immuno-suppression resulting from exposure to dioxin or other toxic herbicides. The Administrator of the VA would then be required to add those disabilities to the list of compensable disabilities, since their service connection would already be presumed. The Academy and the VA would make annual adjustments to the list as more scientific data becomes available.

Finally, the VA would be asked to gather and analyze, on a continuing basis, all clinical data from the health records of veterans examined or treated for disabilities related to dioxin or other toxic herbicides since the enactment of PL 97-72, which mandated treatment for Agent Orange-related health effects. The VA would submit a report on the disabilities treated and the incidence of such disabilities to the House and Senate Veterans' Affairs Committees within one year and would make subsequent semiannual reports.

STATEMENT OF THOMAS E. HARVEY

DEPUTY ADMINISTRATOR OF THE VETERANS ADMINISTRATION

BEFORE THE

HOUSE COMMITTEE ON VETERANS' AFFAIRS

JUNE 8, 1988

It is a pleasure to be here to provide you with an overview of the Veterans Administration's activities regarding Agent Orange.

First, a quick overview. Progress has been achieved in our continuing search for answers and the results that have been obtained thus far are indeed encouraging. In summary, there appears to be a growing scientific consensus that soft tissue sarcomas are not associated with exposure to 2,3,7,8-TCDD, or dioxin, the contaminant of Agent Orange, nor with military service in Vietnam. There is also appearing a consensus that Vietnam veterans are not at increased risk for fathering children with birth defects. The Agent Orange Registry, which now has the results of more than 220,000 physical examinations of Vietnam veterans, still does not show any unusual health patterns among the Vietnam veterans who participated in the registry program. The results of the Air Force's Ranch Hand study which have been released thus far are also encouraging. Those men do not appear to be suffering from any unusual morbidity or mortality patterns. To be sure, there are still some troubling issues that must continue to be examined. Principal among these is the issue of whether non-Hodgkin's lymphoma is associated with exposure to Agent Orange or perhaps with service in Vietnam. Let me now, in more detail, discuss with you the significant research results that I have briefly outlined.

Soft Tissue Sarcomas Studies

In October 1987, the results of the VA/AFIP study entitled "Soft Tissue Sarcoma and Military Service in Vietnam: A Case-Control Study" were published in the Journal of the National Cancer Institute. This case-control study was concerned with men who were of draftable age during the Vietnam conflict and examined the association of soft tissue sarcomas with military service in Vietnam as well with as other host and environmental risk factors. A total of 217 cases of soft tissue sarcomas selected from the Armed Forces Institute of Pathology (AFIP) were compared to 599 controls for Vietnam service, occupational and non-occupational exposure to various chemicals, occupational history, medical history, and life style, for example smoking history and alcohol and coffee consumption. The results of the study indicate that Vietnam veterans, in general, did not have an increased risk of soft tissue sarcomas when compared to those men who had never been in Vietnam. Subgroups of Vietnam veterans who had higher estimated opportunities for Agent Orange exposure seemed to be at greater risk of developing soft tissue sarcomas when their counterparts in Vietnam were taken as a reference group. However, this risk was not statistically significant.

Also, as I will discuss later, the reliance upon military records as an indicator of exposure may now be challenged in light of the results of the TCDD validation study conducted by the Centers for Disease Control.

In a parallel study, the Agent Orange Projects Office, in collaboration with the VA's Pathology Service and the Armed Forces Institute of Pathology (AFIP) reviewed soft tissue sarcoma cases among Vietnam era veterans who had been admitted to VA medical centers during the period 1969 to 1983. The anatomic site, histopathology and relative frequency of soft tissue sarcomas were compared between Vietnam veterans and non-Vietnam veterans. The results of this research show that service in Vietnam had not increased the risk of developing this type of cancer. The findings of the study were published in the _Journal of Occupational Medicine_ in December 1986.

Retrospective Study of Dioxins and Furans in Adipose Tissue

Since 1970, the Environmental Protection Agency (EPA) has been collecting adipose tissue for the monitoring of selected pesticides and since 1983 has been involved in a cooperative research endeavor with the VA to determine the levels of residues of dioxin in the general population. A detailed analysis of tissue specimens from approximately 250 men of the Vietnam era age group is underway. The specimens are being analyzed for 2,3,7,8-TCDD and several other related dioxins and furans to determine if service in the military, especially service in Vietnam, has resulted in increased levels of these compounds as compared to the concentrations in non-veterans of the same age group.

Vietnam Veterans Mortality Study

The results of the VA's "Proportionate Mortality Study of Army and Marine Corps Veterans of the Vietnam War" were released in September 1987. Patterns of mortality among 24,235 Army and Marine Corps Vietnam veterans were compared with that of 25,685 non-Vietnam veterans using standardized proportionate mortality ratios. The veterans were a random sample of deceased Vietnam era veterans identified in a VA computerized benefits file. Military service information was obtained from military personnel records, and cause of death information from death certificates. Statistically significant excess deaths were observed among Army Vietnam veterans for motor vehicle accidents, non-motor vehicle accidents and accidental poisonings. Similar findings have been reported in other studies of Vietnam veterans, including one recently reported by the Centers for Disease Control. Suicides were not more prevalant among Vietnam veterans. Marine Corps, but not Army, Vietnam veterans appeared to have an increased mortality from lung cancer and non-Hodgkin's lymphoma. This study did not investigate possible etiologic factors for these malignancies.

Because there has been some misunderstanding about the release of this study and its proper interpretation, I should like to describe for you the circumstances leading to its acceptance for publication in the Journal of Occupational Medicine. In late 1986, data collection and analysis for the study were completed by the VA's Office of Environmental Epidemiology. The manuscript was submitted to the Journal of the American Medical Association (JAMA) on February 13, 1987. Following that it underwent peer review by scientists selected by JAMA. It should be noted in this regard that peer review is the commonly accepted review process used by the scientific community to assist in establishing the credibility and validity of the research. The process assists in confirming the appropriateness of the study's methodology and the accuracy of the analysis of the researchers. Research flaws are often discovered and corrected by this stringent review process. In light of the possible significance of the findings of the mortality study of a statistical increase in non-Hodgkin's lymphoma and lung cancer in Marine Corps Vietnam veterans who served in the I Corps of Vietnam, it was especially important that this study undergo such a review process prior to its general release.

Following an initial period of review the manuscript was returned to the VA for revision. The comments of the peer reviewers were considered by the investigators and revisions were made in the manuscript and an explanation was provided for not accepting other reviewers' comments. The revised manuscript was returned to JAMA in May 1987. Following a review of the revised manuscript, the VA was advised by JAMA that a decision of non-acceptance for publication had been made.

The mortality study manuscript was subsequently revised and submitted to the Journal of Occupational Medicine (JOM). JOM advised the VA that a peer review would be initiated by that journal. Shortly thereafter, the press learned elsewhere of the study and published a brief article on the results. On August 20, 1987, the manuscript was provided to the Veterans Advisory Committee on Environmental Hazards for scientific review and was discussed during its October 15-16, 1987, meeting. The manuscript was also provided to the Domestic Policy Council's Agent Orange Working Group on September 3, 1987. On November 3, the VA was advised that the manuscript had been accepted for publication by JOM. It is anticipated that the manuscript will be published this month.

Let me provide you with a summary of the comments made by the Science Panel of the Agent Orange Working Group and by the Veterans' Advisory Committee on Environmental Hazards.

The Science Panel found that the study was well executed but criticized the authors for not advising the necessary caution in interpreting the study's findings. The panel determined that this study could not be used to infer anything about the effects of exposure to Agent Orange and agreed with the authors that further work is needed to evaluate causative factors. In regard to the finding of lung cancer in Marine Corps Vietnam veterans, the panel noted that this had not been seen in other studies and that the absence of smoking histories made the interpretation of the data difficult. Finally, the panel believed that the small number of statistical departures from expected mortality could be the result of chance alone.

The Congressionally established Veterans' Advisory Committee on Environmental Hazards concluded that the study was well-designed and well-conducted. The Committee stated that it was their best scientific and professional judgment that the findings concerning the non-Hodgkin's lymphoma and lung cancer, while statistically significant, should be interpreted with caution and are not conclusive. Among the reasons given for this cautionary statement was that a proportionate mortality study by its very nature cannot resolve the question whether the observed results constitute a direct cause-and-effect relationship. A study such as this, the Committee noted, can only lead to the identification of issues requiring further study and analysis. With respect to the lung cancer finding, the Committee also noted the absence of any information about the smoking history of the study's subjects. The Committee recommended no changes in the VA's current guidelines governing the adjudication of claims based upon exposure to dioxin.

In accordance with these recommendations, the VA is conducting five follow-up studies to confirm or complement the findings of the mortality study. First, the VA is updating the mortality study by including an additional 11,000 Vietnam era veterans' deaths in the analysis. These deaths occurred between 1982 and 1984. They will give added statistical power and cases with longer latency periods to the study. This is important because some of the diseases that have been suggested as being associated with Agent Orange exposure or Vietnam service may take a long time to develop. For example, it generally takes as long as 20 years for certain cancers to manifest themselves if they are caused by exposure to environmental chemicals such as Agent Orange. Almost all necessary data have been collected for this analysis.

Second, a separate analysis is planned for Army Vietnam veterans who served in the I Corps area of Vietnam. This is an effort to determine whether the Army veterans who were stationed in the same geographic areas as the Marine Corps veterans experienced mortality patterns similar to the Marines. The U.S. Army and Joint Services Environmental Support Group is assisting the VA in researching Army unit locations in Vietnam for given time periods.

Third, given the widely accepted view of a causal relationship between smoking and lung cancer, a special effort was made to examine military medical records of Marines in the mortality study who died from lung cancer in an attempt to determine their smoking status. The records, however, were not helpful.

Fourth, the VA is reviewing the Patient Treatment File for non-Hodgkin's lymphoma and Hodgkin's disease among Vietnam era veterans who have been treated in VA medical centers. The cases and the control patients will be compared with respect to service in Vietnam and other military service factors. The hypothesis is that if military service in Vietnam is not associated with an increased risk of non-Hodgkin's lymphoma or Hodgkin's disease, then the proportion of veterans having served in Vietnam or having certain military characteristics should be similar for both the cases and the controls.

Finally, a separate mortality study has been designed exclusively for Marine Corps Vietnam veterans. To date, the only study providing an overall mortality rate of the Vietnam veterans is a cohort mortality study recently published by the Centers for Disease Control, but it was restricted to Army veterans. A substantial portion (approximately 20%) of U.S. ground troops in Vietnam were Marines. Unlike the Army units, the Marine Corps units were located in one geographic area, I Corps. In view of the VA mortality study results and the lack of overall mortality rates as well as cause-specific mortality rates for Marine Vietnam veterans, a separate mortality study for Marine veterans will be conducted. The Marine Corps is cooperating fully with the VA in this effort.

Vietnam Veterans Epidemiological Studies - Pub. L. 96-151

As you will recall, Public Law 96-151 mandated that an epidemiological study be performed to determine the effects, if any, of exposure to dioxin. This was amended by Public Law 97-72 to include other possible causes of adverse health effects. In 1983, pursuant to an interagency agreement with the VA, the Centers for Disease Control (CDC) proposed three studies: the Vietnam Experience Study, designed to evaluate the overall impact of military service on Vietnam veterans; the Selected Cancers Study, designed to determine the risks of developing certain types of cancer among Vietnam veterans; and the Agent Orange Exposure Study, intended to assess possible adverse health effects on Vietnam veterans of exposure to the herbicide.

The Vietnam Experience Study is completed and the Selected Cancers Study is proceeding. The Vietnam Experience Study has looked at the health experience of Vietnam and Vietnam era veterans to determine whether Vietnam veterans have health problems different from those who did not serve in Vietnam. In February 1987, the CDC published the findings of a subset of the Vietnam Experience Study. Findings of this study, entitled

"Postservice Mortality Among Vietnam Veterans," indicated that although Vietnam veterans were found to experience a higher rate of postservice mortality than veterans who served elsewhere, this excess of deaths was due primarily to external causes, in other words, to motor vehicle accidents, suicides, homicides, etc. This pattern was similar to the increased mortality patterns due to external causes experienced among World War II and Korean combat veterans.

With respect to the morbidity component of the study, the findings, which were reported in the Journal of the American Medical Association in May, 1988, are the result of an extensive and detailed series of physical, psychological, and laboratory tests. The Centers for Disease Control reports that for most tests, there were no statistically significant differences between Vietnam veterans and non-Vietnam veterans. Vietnam veterans were found to have experienced greater hearing loss and lower sperm concentrations and lower average proportions of morphologically "normal" sperm cells. The CDC reports, however, that despite these last two findings, the average number of children fathered per veteran in each group was identical, 1.6 children. Psychological problems did appear to be more prevalent among Vietnam veterans than non-Vietnam veterans. A significant finding in this regard is that 2% of Vietnam veterans still experience episodes of post-traumatic stress disorder up to twenty years after their service in Vietnam. With respect to reproductive outcomes, Vietnam veterans reported more adverse reproductive and child health outcomes than non-Vietnam veterans during their telephone interview. However, on examination of hospital birth records, the children of Vietnam veterans were no more likely to have have birth defects (all types combined) recorded than were children of non-Vietnam veterans.

The Selected Cancers Study is focusing on whether Vietnam veterans are at increased risk of developing certain cancers which have been identified in the scientific literature as possibly associated with exposure to phenoxy herbicides and their dioxin contaminant. The cancers are: lymphoma, soft tissue sarcoma, nasal and naso-pharyngeal cancer, and primary liver cancer. The CDC reports that results from that study will be published in 1990.

With respect to the Agent Orange Exposure Study, I must report that this study cannot be done. Since 1980, the Veterans Administration, other Federal agencies, and contractors have attempted to design a satisfactory epidemiological study in fulfillment of the mandate to study the effects of exposure to

Agent Orange. The difficulty is and has always been the inability to discriminate between exposed and unexposed ground troops. A variety of methods were employed in trying to address this problem. None of these attempts has been successful for several reasons:

(1) Military records lack sufficient detail to locate accurately an individual with respect to an area of Agent Orange usage with the exception of those men in the Air Force unit called Ranch Hand, men who directly handled the herbicide in preparing for and in flying aircraft runs to spray it. They are being studied carefully and repeatedly by the Air Force in a continuing research effort. The Congressional Office of Technology Assessment and the Science Panel of the Agent Orange Working Group have agreed that military records cannot be used as a basis for determining individual exposure.

(2) Self-reporting by Vietnam veterans of exposure cannnot be used because troops were exposed to a variety of aerial sprayings thereby making it impossible for an individual to discriminate among the sprayings of Agent Orange, other herbicides, and insecticides.

The inability to evaluate exposure by other means led to a decision to use measurements of retained TCDD as a means of identifying exposure. TCDD (2,3,7,8-TCDD), a contaminant of Agent Orange, is retained in body fats after exposure to the herbicide and can be detected in the fats found in blood as well as in other body fats. Technical advances in assay techniques have made it possible to measure minute amounts of TCDD in human blood. The CDC utilized the technique to determine that the chemical persists in elevated amounts among individuals who were exposed to Agent Orange as Ranch Hand personnel and a group of persons exposed to TCDD in Missouri or in chemical plants.

The CDC has determined the TCDD content of blood from 646 Vietnam ground troop veterans and 97 "non-Vietnam" veterans matched to their contemporaries who had served in that country. The results demonstrated that the TCDD content was essentially the same whether a man was in Vietnam as a ground combatant or was never in that country. It was thus impossible to use the blood content of TCDD to identify a group or cohort of Vietnam ground troop veterans who had been exposed to Agent Orange.

In contrast to the ground troops, Air Force veterans of the Ranch Hand operation had blood content of TCDD that was several fold greater. There was, however, considerable variation from one Ranch Hand veteran to another. It thus is obvious that exceptional exposure to Agent Orange as long as twenty years ago would be detected in ground troops had it occurred. The CDC tells us that the so-called half-life (i.e., the period in which 50 percent of the chemical is eliminated through disintegration) of TCDD in humans is about 7 years which means that even a small excess 20 years ago would be detected today. These results make it exceedingly unlikely that any method will satisfactorily distinguish between exposed and unexposed Vietnam veterans. Therefore, a scientifically meaningful epidemiological study of the possible health effects of Agent Orange cannot be conducted.

Related Activities

Public law 96-151 required the Administrator to conduct a comprehensive review and analysis of the world-wide scientific literature relating to possible adverse health effects from exposure to the phenoxy herbicides or dioxins. In 1981, the VA published a two-volume Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins. Because of continued active research, a two-volume update covering the literature through December 1983 was published in 1984. Each year since that time the review has been updated. Volumes Eleven and Twelve are now in publication. Lay language synopses have also been prepared on volumes one through ten of these publications for review and use by the general public.

These publications are routinely shared by the VA with Congress, all major VA health facilities' Environmental Physicians and hospital libraries, VA Regional Offices, the VA's Advisory Committee on the Health Related Effects of Herbicides, the Veterans' Advisory Committee on Environmental Hazards, the Domestic Policy Council's Agent Orange Working Group and its science panel, and with the governments of Australia, Italy, and New Zealand. Copies are also made available to veterans, State Agent Orange programs, and the general public upon request.

The VA continues to offer concerned Vietnam veterans a comprehensive physical examination as part of its Agent Orange Registry program. Approximately 228,000 Vietnam veterans have received examinations. Additionally, Vietnam veterans continue to be eligible for health care under the authority of Public Law 97-72 for any condition that may have been caused by exposure to dioxin or to a toxic substance in a herbicide or defoliant used in Vietnam.

Public Law 98-542, the "Veterans Dioxin and Radiation Exposure Compensation Standards Act," required the VA to specify standards for deciding compensation claims based upon exposure to Agent Orange or to ionizing radiation from participation in the nuclear weapons testing program or as a result of service with the occupation forces of Hiroshima or Nagasaki, Japan. The Act also required that a new Veterans' Advisory Committee on Environmental Hazards be created and consist of four lay members and eleven scientific members. The Committee reviews the scientific literature and provides comments and recommendations to the Administrator concerning administrative and legislative initiatives.

In August 1985, following a period of public comments and consultation with the Advisory Committee on Environmental Hazards, the VA published final regulations for the adjudication of claims based upon exposure to Agent Orange (and to ionizing radiation). Under the regulations, which also contain criteria the Agency will employ in evaluating scientific studies, chloracne, a skin disorder, will be presumptively service-connected if manifested within three months of the veteran's departure from Vietnam. The Agency also specifically found that sound scientific and medical evidence does not establish a cause and effect relationship between dioxin exposure and porphyria cutanea tarda (a liver disorder), soft tissue sarcoma, or any other disease except chloracne. Continued review of the medical and scientific evidence by the Advisory Committee has led it to maintain the same position.

Conclusion

In conclusion, I would like to emphasize that the Veterans Administration has addressed the Agent Orange controversy forthrightly and aggressively. The long-awaited research results are now becoming available, and the parts of the Agent Orange puzzle are begining to present a clear picture. Some preliminary conclusions are encouraging. Based upon the currently available information, it appears that Vietnam veterans did not have substantial opportunity for significant exposure to Agent Orange. Careful studies have failed to detect any relation between birth defects in children and Vietnam service or exposure of fathers to the components of Agent Orange.

Evidence for an association between exposures to phenoxy herbicides, including Agent Orange, or the contaminant 2,3,7,8-TCDD and malignancies remains conflicting. Recent evidence strongly suggests that soft tissue sarcomas are not causally related to exposure to phenoxy herbicides or military service in Vietnam. Recent evidence regarding a causal association between herbicide exposure and non-Hodgkin's lymphoma is inconclusive. Further work is being done on this issue. The growing and mounting scientific evidence does not support any change in compensation policy at this time. While the pieces of the puzzle continue to come into focus, we will continue to offer medical care and services under the authority of Public Law 97-72 to eligible Vietnam veterans for those conditions that may possibly be related to exposure to Agent Orange notwithstanding the absence of any scientific evidence of a causal association. That is an obligation which we shall strive to meet with compassion and understanding. Our Vietnam veterans deserve no less.

THE HONORABLE DON NEWMAN
CHAIRMAN
DOMESTIC POLICY COUNCIL. AGENT ORANGE WORKING GROUP

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE, GOOD MORNING! I AM DON NEWMAN, CHAIRMAN OF THE DOMESTIC POLICY COUNCIL AGENT ORANGE WORKING GROUP.

AS YOU KNOW, SINCE 1979 THE WORKING GROUP HAS SERVED A COORDINATING ROLE WITHIN THE GOVERNMENT. IN ADDITION TO FACILITATING DISCUSSIONS AMONG FEDERAL AGENCIES AND DEPARTMENTS REGARDING AGENT ORANGE RESEARCH DIRECTION, IT HAS ASSURED SCIENTIFIC PEER REVIEW OF PROTOCOLS AND SUBSEQUENT STUDIES.

I AM PROUD TO REPRESENT AN ADMINISTRATION THAT HAS FOCUSED THE HIGHEST LEVELS OF GOVERNMENT RESEARCH ON THE HEALTH OF VIETNAM VETERANS.

AS YOU KNOW, AFTER ALMOST TEN YEARS AND THE EXPENDITURE OF $90 MILLION DOLLARS ON SCIENTIFIC RESEARCH OF VETERANS BY SEVERAL AGENCIES, WE CAN NOW SHARE WITH YOU THE RESULTS OF PEER REVIEWED STUDIES WHICH WILL GIVE US, THE CONGRESS, AND VIETNAM VETERANS, CAUSE TO BE REASSURED THAT THEIR SERVICE IN VIETNAM AND POSSIBLE EXPOSURE TO AGENT ORANGE ARE NOT RESULTING IN SIGNIFICANT ADVERSE HEALTH AFFECTS EXCEPT PSYCHOLOGICAL PROBLEMS.

THE VETERANS ADMINISTRATION, DEPARTMENT OF DEFENSE (UNITED STATES AIR FORCE) AND CENTERS FOR DISEASE CONTROL WILL PROVIDE YOU DETAILS OF THE STATUS AND FINDINGS OF THE KEY STUDIES OVER WHICH THE AOWG HAS HAD OVERSIGHT. THE PROTOCOLS FOR EACH OF THESE STUDIES AND THE SUBSEQUENT CONCLUSIONS WHERE AVAILABLE HAVE UNDERGONE THOROUGH SCIENTIFIC PEER REVIEW.

THEY ARE:

THE DOD RANCH HAND STUDY (USAF)
THE CDC VIETNAM EXPERIENCE STUDY
THE CDC STUDY OF SELECTED CANCERS
THE CDC AGENT ORANGE STUDY
THE VA MORTALITY STUDY AND OTHER RELATED STUDIES

THE KEY POINT I WISH TO MAKE TODAY IS THAT IN THE STUDIES WHICH HAVE COME TO CONCLUSION, WE ARE SEEING NO CAUSE-EFFECT RELATIONSHIP BETWEEN SERVICE IN VIETNAM AND POSSIBLE EXPOSURE TO AGENT ORANGE AND ADVERSE HEALTH. THE STUDIES CONCERNING THE GROUND TROOPS SHOW NO INCREASE IN DIOXIN LEVELS IN THESE TROOPS. SCIENTIFIC EVIDENCE DOES NOT SUPPORT THE CLAIM THAT MAJOR INCREASES IN ILL HEALTH ARE CAUSED BY EXPOSURE TO AGENT ORANGE. AS YOU WILL HEAR IN OTHER TESTIMONY, IT DOES NOT NOW APPEAR THAT THE AVERAGE VIETNAM VETERAN IS AT RISK DUE TO AGENT ORANGE EXPOSURE.

WE ARE NOT SAYING THAT NO ONE WAS EXPOSED IN VIETNAM. IN FACT AS DR. JAMES MASON, DIRECTOR OF CDC WILL TESTIFY, WE KNOW THAT SPECIAL GROUPS WHOSE OCCUPATION BROUGHT THEM INTO FREQUENT CONTACT WITH AGENT ORANGE (SUCH AS RANCH HANDERS) DO HAVE HIGHER LEVELS OF DIOXIN IN THEIR BLOOD. THE CENTERS FOR DISEASE CONTROL'S MORBIDITY AND MORTALITY WEEKLY REPORT OF MAY 27, 1988 INDICATED THAT OF 147 RANCH HANDERS EXAMINED, 62% HAD TCDD

LEVELS HIGHER THAN 20 PARTS PER TRILLION (PPT), THAT THEY HAD A MEAN SERUM LEVEL OF 49 PPT AND THAT THE FIVE HIGHEST HAD AS MUCH AS FROM 201 TO 313 PPT. 20 PPT IS A GENERALLY ACCEPTABLE LEVEL IN THE GENERAL POPULATION. BUT EVEN AFTER THE MOST INTENSIVE PHYSICAL EXAMINATION, THESE, SO FAR, HAVE SHOWN FEW ILL EFFECTS AND THEY CONTINUE TO BE CAREFULLY MONITORED.

FOR THE MAJORITY OF VIETNAM VETERANS, IT IS CORRECT TO SAY THAT OTHER THAN SOME PROBLEMS RELATED TO STRESS, IT DOES NOT NOW APPEAR THAT THEY ARE AT RISK DUE TO AGENT ORANGE EXPOSURE. I, THEREFORE, TAKE THE POSITION THAT IT IS NOT SOUND PUBLIC POLICY TO MAKE SWEEPING PRESUMPTIONS WHICH APPEAR TO BE BASED ON FRUSTRATION OR THE LACK OF SCIENTIFIC EVIDENCE TO SUPPORT DESIRED CONCLUSIONS.

THE GOVERNMENT OF AUSTRALIA WHICH ESTABLISHED A ROYAL COMMISSION SOME YEARS AGO TO EXAMINE THE ENTIRE QUESTION OF AGENT ORANGE EXPOSURE RELATIVE TO THE VIETNAM SERVICE OF THEIR TROOPS, IS RE-EXAMINING THE ISSUE. IN A TWENTY-TWO ITEM TELEGRAM WE RECEIVED FROM OUR EMBASSY IN AUSTRALIA, IT WAS REPORTED TO US THAT THE MINISTER FOR VETERANS AFFAIRS ADDRESSED PARLIAMENT ON MAY 19, 1988 ON THE CONCLUSIONS OF THEIR ROYAL COMMISSION WHICH HAVE BEEN EVALUATED BY THEIR NATIONAL SCIENCE INSTITUTE OR COUNCIL. THE CONCLUSIONS REACHED ARE ALMOST IDENTICAL TO THOSE OF OUR OWN EXHAUSTIVE STUDIES AND ARE SIMILAR IN RESULT WITH REGARD TO STRESS, BIRTH DEFECTS AND EXPOSURE. THEIR EMPHASIS IS WELL STATED IN THE SUMMATION "THE GOVERNMENT BELIEVES THAT TOO MANY VIETNAM VETERANS' LIVES HAVE BEEN DISRUPTED BY FEARS ABOUT AGENT ORANGE AND OTHER CHEMICALS. IN ENDORSING THE VIEW THAT ANY EXPOSURE OF AUSTRALIANS TO CHEMICAL AGENTS IN VIETNAM WOULD BE UNLIKELY TO CAUSE LONG TERM ADVERSE HEALTH EFFECTS, THE GOVERNMENT IN NO WAY STEPS ASIDE FROM ITS COMMITMENT TO HELP VETERANS."

THE US NEWS AND WORLD REPORT OF MAY 23, 1988 SAID IT BEST WHEN IT QUOTED MARY STOUT, PRESIDENT OF VIETNAM VETERANS OF

AMERICA AS SAYING "THE CDC VIETNAM EXPERIENCE STUDY RESULTS PROVED THE RESILIENCY OF MOST OF THOSE WHO WENT TO VIETNAM AND RETURNED. THERE IS A CERTAIN STRENGTH FROM PEOPLES' EXPERIENCE IN WAR. IT HELPS THEM TO DEAL WITH THE FACT THAT THEY GO THROUGH A LOT OF STRESS, AND IT HELPS THEM TO MAINTAIN A FAMILY, A HOME AND A JOB".

I REGRET, THAT I HAVE ANOTHER MEETING TO ATTEND, BUT, DR. MASON WHO AT ONE TIME ACTED AS CHAIR OF THE AOWG HAS MY FULL CONFIDENCE AND CAN ANSWER THE SCIENTIFIC QUESTIONS FOR ME AND WITH HIM IS DR. HART, THE CHAIR OF THE AOWG SCIENCE PANEL.

THANK YOU MR. CHAIRMAN.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control

FOR RELEASE ONLY UPON DELIVERY

Testimony of

James O. Mason, M.D., Dr.P.H.
Director, Centers for Disease Control
U.S. Public Health Service

DEPARTMENT OF HEALTH AND HUMAN SERVICES

before the

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON VETERANS' AFFAIRS

SUBCOMMITTEE ON
HOSPITALS AND HEALTH CARE

Wednesday, June 8, 1988

9:00 a.m.

Room 334, Cannon House Office Building

INTRODUCTION

Good morning, Mr. Chairman, I am Dr. James O. Mason, Director, Centers for Disease Control (CDC). I welcome this opportunity to appear before this Subcommittee to describe the progress of the studies of the health of Vietnam veterans being conducted by the Centers for Disease Control.

With me this morning is Dr. Vernon Houk, Director of CDC's Center for Environmental Health and Injury Control, who has had oversight responsibility for these studies since their initiation.

BACKGROUND

Public Laws 96-151 and 97-72 directed the Veterans Administration (VA) to conduct investigations of Vietnam veterans' health. The first of these laws, signed in December 1979, required a study to assess the possible health effects of exposure to herbicides, primarily Agent Orange, during the Vietnam conflict. The second, signed in November 1981, expanded the scope of the study to allow for the inclusion of other environmental hazards associated with service in Vietnam. CDC was assigned the responsibility for design and conduct of the studies in January 1983 by an Interagency Agreement with the Veterans Administration (VA). CDC also conducted a Birth Defects Study among Vietnam veterans, which was a separate research effort supported by Department of Defense (DOD), the VA, and CDC. The results of that study were published in 1984 and have been previously reported to you.

In May of 1983, CDC completed and submitted a draft research protocol for scientific review and comment by four groups: the Office of Technology Assessment (OTA), the Science Panel of the Cabinet Domestic Policy Council Agent Orange Working Group (AOWG), the HHS Advisory Committee on Special Studies Relating to the Possible Long Term Effects of Phenoxy Herbicides and Contaminants (the Ranch Hand Panel), and CDC's own Ad Hoc Review Panel. The CDC received comments from these groups by September 1983.

The final protocol for these studies was published in November 1983. It incorporated modifications suggested by the scientific reviews and stated that the studies were designed to allow for the addition of procedures or questions based on interim analyses of the data or data from sources outside these studies. Three independent but related studies comprise CDC's Agent Orange Projects:

1. The Vietnam Experience Study: a study of the long-term health effects of military service in Vietnam.
2. The Agent Orange Study: a study of the long-term health effects of exposure to herbicides in Vietnam.
3. The Selected Cancers Study: a study to determine the risks of specific cancers among Vietnam veterans.

I will summarize the status of these three studies, beginning first with the Selected Cancers Study.

STATUS OF THE SELECTED CANCERS STUDY

The Selected Cancers Study was designed to evaluate if Vietnam veterans are at increased risk of developing certain cancers which have been identified in the scientific literature as possibly associated with industrial or occupational exposure to phenoxy herbicides or chlorophenols and their dioxin contaminant. These cancers are: lymphoma (including Hodgkin's disease and non-Hodgkin's lymphomas), soft tissue sarcoma, nasal and nasopharyngeal cancer, and primary liver cancer.

This case-control study was designed because the sample sizes of the proposed cohort studies (the Vietnam Experience and Agent Orange Studies) were not large enough to provide answers about these relatively rare cancers. Case ascertainment by the eight participating cancer registries began in December 1984 and will continue through November 1988. The controls are selected from the same eight geographic areas through a random digit dialing process. As cases and controls are identified, it is not known whether they are military veterans and, if they are veterans, whether they served in Vietnam. That information is obtained during the interview process along with other data on risk factors for these cancers.

As of March 31, 1988, interviews have been completed on approximately 2100 cases and 1700 controls. The interviews and validation of diagnosis by pathology tissue review will be completed in the summer of 1989. Data analysis should be completed in late 1989 and the results published in 1990.

Next, I will address the Agent Orange Study.

STATUS OF THE AGENT ORANGE STUDY

The Agent Orange Study was designed to evaluate the possible health effects of exposure to Agent Orange in Vietnam veterans. The implementation of the Agent Orange study was dependent on the development of a scientifically valid herbicide exposure index based on information contained in military records. As cautioned in the 1983 protocol, since many of the proposed categorization procedures were untested, pilot study assessments were necessary before a final decision could be made to proceed with a full-scale study.

As a result of intensive work between 1983 and 1986 by the U.S. Army and Joint Services Environmental Support Group and CDC, a Science Subpanel of the Agent Orange Working Group concluded in June 1986 that a "scientifically valid study based on military records was not possible without an independent method of exposure verification." During early 1986 CDC had already begun work to develop a new laboratory method utilizing blood to establish current body burdens of dioxin as an indicator of previous exposure to dioxin-containing substances such as Agent Orange. The CDC scientists were successful and this new method, utilizing blood serum, is a more feasible approach for testing groups of individuals than previous methods, which measured dioxin in adipose (fat) tissue. A protocol for a "Validation Study Comparing Military Records-based Estimates of the Likelihood of Exposure to Agent Orange with Current Serum Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)" was developed by CDC and approved by the AOWG Science Panel and OTA in October 1986.

The results of this Validation Study, released in July 1987, showed no association between serum TCDD levels and several different military records-based estimates of the likelihood of Agent Orange exposure. Also, there was no association between TCDD levels and self-reported exposure obtained directly from the veteran. Among the 646 Vietnam veterans for whom TCDD levels were obtained, the median TCDD level was 3.8 parts per trillion (ppt), with a range from less than 1 to 45 ppt. The median TCDD level for the 97 non-Vietnam veterans was also 3.8 ppt, with a range from less than 1 to 15 ppt. Nine Vietnam veterans (about 1% of the sample) and 3 non-Vietnam veterans (about 3% of the sample) had current TCDD levels greater than 10 ppt (ATTACHMENT A). Two Vietnam veterans had levels above 20 ppt, one with 25 and another with 45 ppt; no non-Vietnam veterans had levels above 20 ppt. The veteran with a level of 45 ppt reported no exposure (military or civilian) to herbicides; the veteran with a level of 25 ppt reported 180 days of indirect military exposure (defined as walking through, or clearing vegetation in, a previously sprayed area), plus one day of home use, but no other exposure. During the telephone interview, both of these men reported their health as "excellent," with no health problems perceived as a consequence of exposure to Agent Orange.

The methods CDC used for selecting individuals and classifying herbicide exposure in this TCDD Validation Study have been criticized, particularly by persons associated with the New Jersey Pointman project. The focus of the criticism is the so-called "hits" model used for selecting men into the study. This model computes for each veteran a "hits score"--the sum of all the occasions for which a veteran's company was within 2 kilometers of an area sprayed by Agent Orange in the previous 6 days. (A higher score in this model means a greater opportunity for exposure.) If we had only evaluated the "hits" model, the critics would be correct. However, we also compared serum TCDD levels with several other exposure models, including two which are similar to those being used by the New Jersey group. One such model is the number of days a man spent in any of the five most intensely sprayed areas, and the other is the amount of direct or indirect exposure reported by the veteran himself. For example, 25% of our study group said they had been directly exposed. These men, including those reporting current health problems, showed TCDD levels no higher than the others. A final point to consider in evaluating the potential for exposure in this group of 646 Vietnam veterans is that they served an average of 320 days in tactical battalions which operated in the heaviest sprayed area of Vietnam (III Corps) during the peak years of Agent Orange spraying (1966-1969).

At the same time the Validation Study was being carried out, CDC was measuring TCDD levels on a group of Air Force Health Study participants (which consists of Ranch Handers and a comparison group) in the U.S. Air Force and CDC study of the half-life (the time it takes the body to eliminate half of a substance) of TCDD. Of the 147 Ranch Handers whose TCDD values were measured, 25 had current TCDD levels of between 50-100 ppt, 16 between 100-200 ppt, and 5 over 200 ppt; all but one of the 49 veterans in the comparison group had TCDD values less than 10 ppt (ATTACHMENTS B and C). The Air Force/CDC Half-Life Study, a National

Institute for Occupational Safety and Health (NIOSH) Pilot Study of herbicide production workers, and the New Jersey Pointman Project have all detected substantially elevated TCDD levels in occupationally exposed individuals whose last known exposure occurred 15 to 20 or more years ago.

The published results from New Jersey's project are also consistent with findings from CDC's TCDD Validation Study in that participants in the New Jersey study who did not handle Agent Orange directly as an occupational duty did not have elevated TCDD levels upon examination in 1987. The measurement of adverse health effects in those who were exposed sufficiently to have TCDD levels still elevated at present is being carried out in the Air Force Health Study and NIOSH studies, where such individuals are being carefully and, in the case of Air Force Health Study, repeatedly examined, including individual serum TCDD levels being measured by CDC.

As a result of their reviews, both AOWG and OTA concluded in September 1987 that it is not possible to design a large scale epidemiologic study to look for effects of Agent Orange in ground troops who served in Vietnam. Accordingly, AOWG instructed CDC to begin the process of canceling the data collection contracts and closing out all activities related to the Agent Orange Study. CDC is currently negotiating the settlement costs with the contractors related to the termination of this study.

Last, I will summarize the status of the Vietnam Experience Study.

STATUS OF THE VIETNAM EXPERIENCE STUDY (VES)

The Vietnam Experience Study was designed to evaluate possible health effects of the "general Vietnam experience" by comparing the health status of a cohort of male U.S. Army veterans who served in Vietnam with a cohort of male U.S. Army Vietnam-era veterans who served elsewhere. This study was initially designed with three main components: a mortality assessment, telephone interviews, and medical and psychological examinations. Based on interim analyses of the data and the experience of the Ranch Hand Study (related to acquisition of birth records), CDC added to the Vietnam Experience Study a birth outcome validation component and a semen analysis component.

I will describe the general findings of the Vietnam Experience Study, starting with the Mortality Assessment component, which was published in February 1987. Then, I will address the morbidity findings which were published in the Journal of the American Medical Association on May 13, 1988. It is important to note that we had originally planned to publish the morbidity findings sequentially as the various components were completed. However, we subsequently decided, with input from Congressional staff and OTA, to publish the results simultaneously. This decision was made because of concerns related to releasing self-reported interview data separately from the medical examination and birth outcome validation data.

Mortality Assessment Component of the VES

The Vietnam Experience Study used a random sample of military records to find 9,324 male U.S. Army veterans who served in Vietnam and 8,989 Army veterans who served in Korea, Germany, or the United States during the same time period. All of these men had been discharged alive with a rank of E1-E5 after a single enlistment starting between 1965 and 1971.

Over the entire follow-up period (from discharge through December 1983), total mortality among the Vietnam veterans was 17% higher than for the other veterans. The excess mortality occurred mainly in the first 5 years after discharge from active duty, when the death rate among Vietnam veterans was about 45% higher than the rate of non-Vietnam veterans. Most of the increased mortality was from external causes, such as motor vehicle injuries, suicide, and homicide. After the first 5 years, mortality among Vietnam veterans was similar to that of non-Vietnam veterans, except for drug related deaths, which continued to be elevated.

The overall finding of excess postservice mortality due to external causes among Vietnam veterans was similar to that found among men returning from combat areas after World War II and the Korean War. An unexpected finding in this study was the lower rate in deaths from diseases of the circulatory system among Vietnam veterans compared to non-Vietnam veterans.

As mentioned above, the first mortality report includes deaths identified through 1983. We have recently updated this through 1986. With the exception of the first 5 years following discharge from military service, Vietnam veterans continue to have a similar rate of all-cause mortality (rate/1000=1.7) compared to non-Vietnam veterans (rate/1000=1.8). A complete cause of death analysis which includes these additional years, 1984-1986, should be completed by August 1988.

Morbidity Findings of VES

Attached to my testimony is a summary table of the significant findings from this component of the Vietnam Experience Study (ATTACHMENT D). In presenting these findings, I would like to point out that there are no comparable morbidity data from previous wars, as there was for mortality data. Therefore, it is not possible to compare morbidity data from the Vietnam Experience Study with data on veterans of previous wars. I will discuss the findings of the telephone interview, the medical and psychological examination, and the reproductive and child health components of this study.

Telephone Interview:

In the telephone interview component, nearly 18,000 veterans (whose addresses on their military records date from the late 1960s) were traced with 94% of the Vietnam and 92% of the non-Vietnam men located during 1985-1986. Of the men located, 93% of the Vietnam and 91% of the non-Vietnam men were interviewed, a tribute to their extraordinary spirit of cooperation.

The interviews revealed a broad similarity between the two groups in terms of current demographic and social characteristics, such as education, income, employment rates, and marital status. Although the two groups are very similar socioeconomically, the Vietnam veterans reported more current limitations in activities, more current use of prescription drugs, and a greater prevalence of many types of diseases and somatic and psychological symptoms. Also, while this study was not large enough to evaluate risks of specific types of cancers, the two groups were similar in the total reported number of physician-diagnosed cancers. The Vietnam veterans reported more problems with impaired fertility, yet both groups reported fathering the same average number of children. The Vietnam veterans also reported more birth defects and other health problems among their children. The verification of these findings is addressed later in this testimony.

Medical and Psychological Examinations:

In the examination component, we invited a random subsample (approximately 42%) of interviewed men for comprehensive physical, psychological, and laboratory examinations. Physical and laboratory examinations showed few current differences between the two groups, despite the many differences elicited by telephone interview. For example, there were large differences in skin problems reported during the telephone interview, but on examination all skin conditions, including scars from possible past chloracne, were found with similar frequency. Skin examinations were carried out by board-certified dermatologists who were not told whether the man being examined was a Vietnam or a non-Vietnam veteran.

Psychological evaluation of the men who were examined was done through standardized interviews and questionnaires. Although most men in both groups fell within normal limits in these evaluations, current psychological problems [primarily alcohol abuse or dependence (13.7% versus 9.2%), anxiety (4.9% versus 3.2%), or depression (4.5% versus 2.3%)] were more prevalent among Vietnam than non-Vietnam veterans.

Analysis of combat-related post-traumatic stress disorder was limited to Vietnam veterans. About 15% of these veterans reported ever experiencing symptoms which met diagnostic criteria for this disorder. Combat-related psychological symptoms diminished over time, but 2% still experienced episodes of post-traumatic stress disorder during the month before examination, up to 20 years after their service in Vietnam.

Overall, hundreds of physical health items were evaluated as part of the examinations, including blood pressure, electrocardiograms, Doppler examinations of peripheral arteries, chest roentgenograms, and pulmonary function tests, visual acuity and hearing tests, peripheral nerve function, immunologic status, and over 100 laboratory assays. For most items, no statistically significant differences were found between the two groups. The most noteworthy differences were hearing loss, stool occult blood, evidence of past infection with hepatitis B, lower sperm concentrations, and lower average proportions of morphologically "normal" sperm cells. Despite these last two findings, the average number of children fathered per veteran in each cohort after assignment to primary tour of duty was identical--1.6 children.

Reproductive Outcome Findings of the VES

Although Vietnam veterans reported more adverse reproductive and child health outcomes than non-Vietnam veterans during the telephone interview, the children of Vietnam veterans were no more likely to have birth defects (all types combined) recorded on hospital birth records than were children of non-Vietnam veterans. These results are consistent with the findings of three epidemiologic studies (the Australian birth defect

INTENTIONAL
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study, the CDC birth defects study, and the U.S. Air Force Ranch Hand Study) conducted since 1981 on the relationship of Vietnam service and birth defects in children of male veterans. In addition, the recently published study of birth defects in the Seveso, Italy, area, which was contaminated by TCDD in 1976, concluded "that the data collected contain no evidence to support the position that in the population of the Seveso area exposed to TCDD, there was greater risk of producing congenitally malformed offspring." However, the authors cautioned that "the number of exposed pregnancies was not big enough to detect a low and specific teratogenic risk increase."

National Institute for Occupational Safety and Health Production Workers Study.

The National Institute for Occupational Safety and Health is doing a cohort mortality study and maintains a registry of approximately 7,000 workers who were employed at 14 plants in the production of chemicals that were contaminated with 2,3,7,8-TCDD. This study should be completed in FY 1989.

In addition, NIOSH is doing a cross-sectional morbidity study of workers from 2 of these 14 plants. This study will include data from interviews of approximately 350 production workers with occupational risk of high exposure and from physical examinations of about 275 of the workers interviewed. Blood concentrations of TCDD will be measured to determine the probable extent of exposure to TCDD. TCDD levels are also being measured on a comparison group of unexposed individuals matched on age, sex, race, and neighborhood. Based on hyphotheses already in the published literature of animal and human studies related to dioxin exposure, the NIOSH study has been designed to identify effects of exposure to TCDD on reproductive, hepatic, neurologic, immunologic, and psychologic disorders. This study is to be completed in FY 1990.

Specific Conditions Related to Pending Legislation

I am aware of pending legislation proposing that lung cancer, non-Hodgkin's lymphoma, and certain undefined immunodeficiency syndromes be considered as compensable in Vietnam veterans. In presenting the data in these areas from the Vietnam Experience Study, I want to caution that the number of specific types of cancer are too few for drawing conclusions.

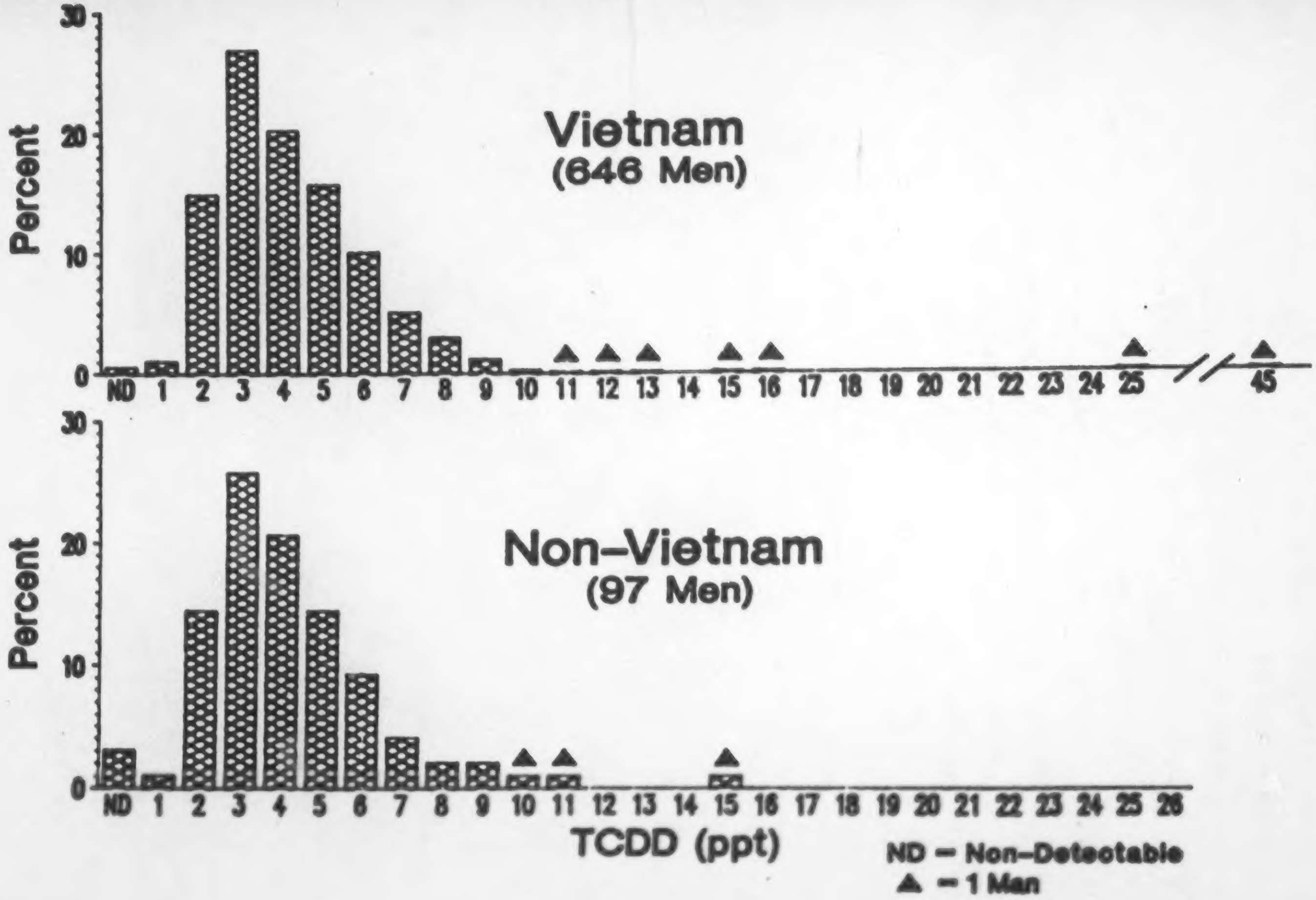
For non-Hodgkin's lymphoma, seven confirmed cases were identified in the Vietnam group compared to one confirmed case in the non-Vietnam group. Also, one confirmed lung cancer case was identified in the Vietnam group compared to two confirmed lung cancer cases in the non-Vietnam group. These numbers differ slightly from those reported during the May 12, 1988 Senate hearings and represent the current data from the Vietnam Experience Study based on the recent completion of medical record reviews. Additional cases may be identified in future mortality updates of these cohorts.

Additionally, we tested all of the examined men for cell-mediated immuno-deficiency and laboratory assays of T & B lymphocytes, and found no evidence of any differences between the Vietnam and non-Vietnam groups in these immune system measurements.

In addition to the articles in the Journal of the American Medical Association, CDC is publishing a multi-volume monograph on the Vietnam Experience Study. These documents, containing thousands of pages, provide a comprehensive, detailed summary of the data collection procedures, study methods, and results for this study. These documents are currently being edited and we will provide them as soon as they are printed, probably in August. However, I am submitting at this time the first volume, which is a synopsis of the study, that expands on the published reports in the JAMA. In addition, I am submitting the detailed analysis of the Validation Study to the Committee.

This concludes my testimony.

ATTACHMENT A



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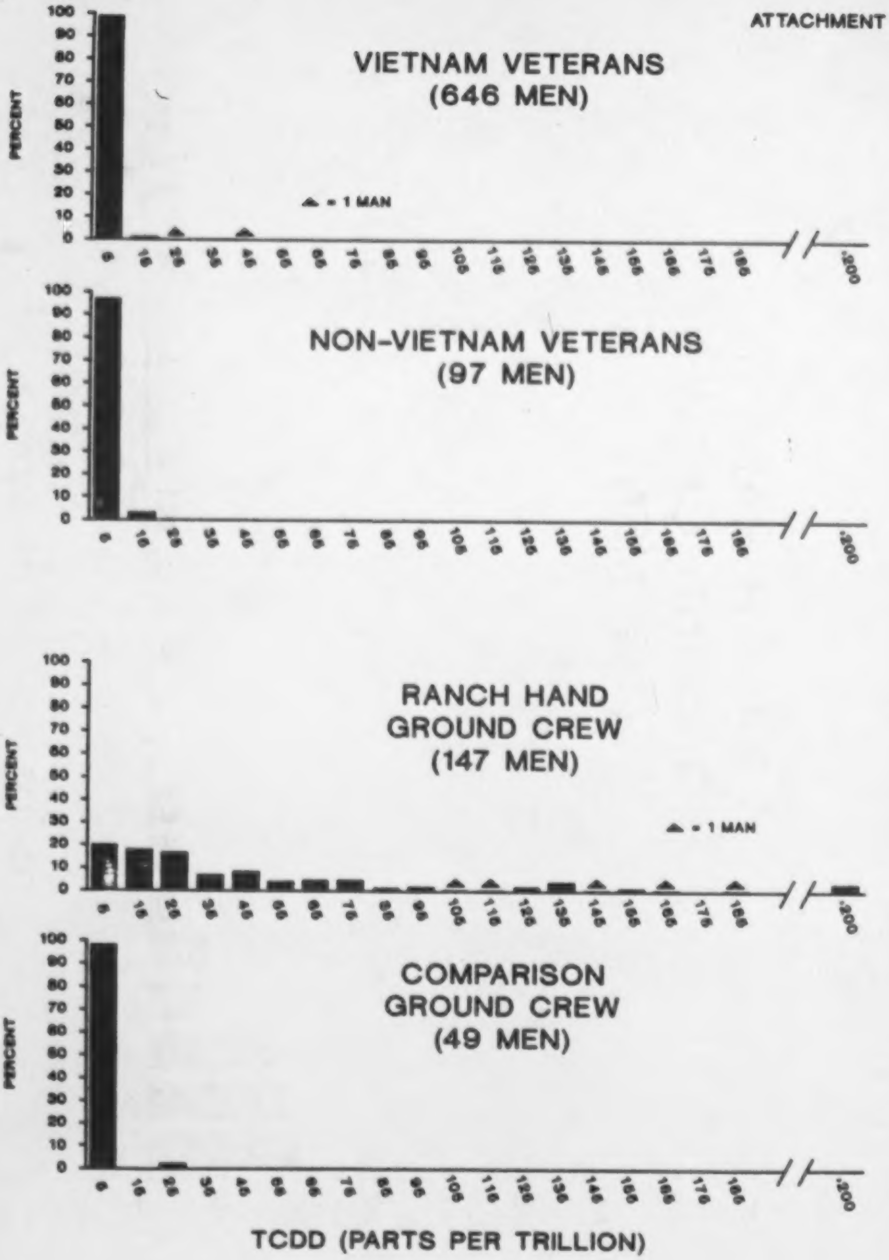
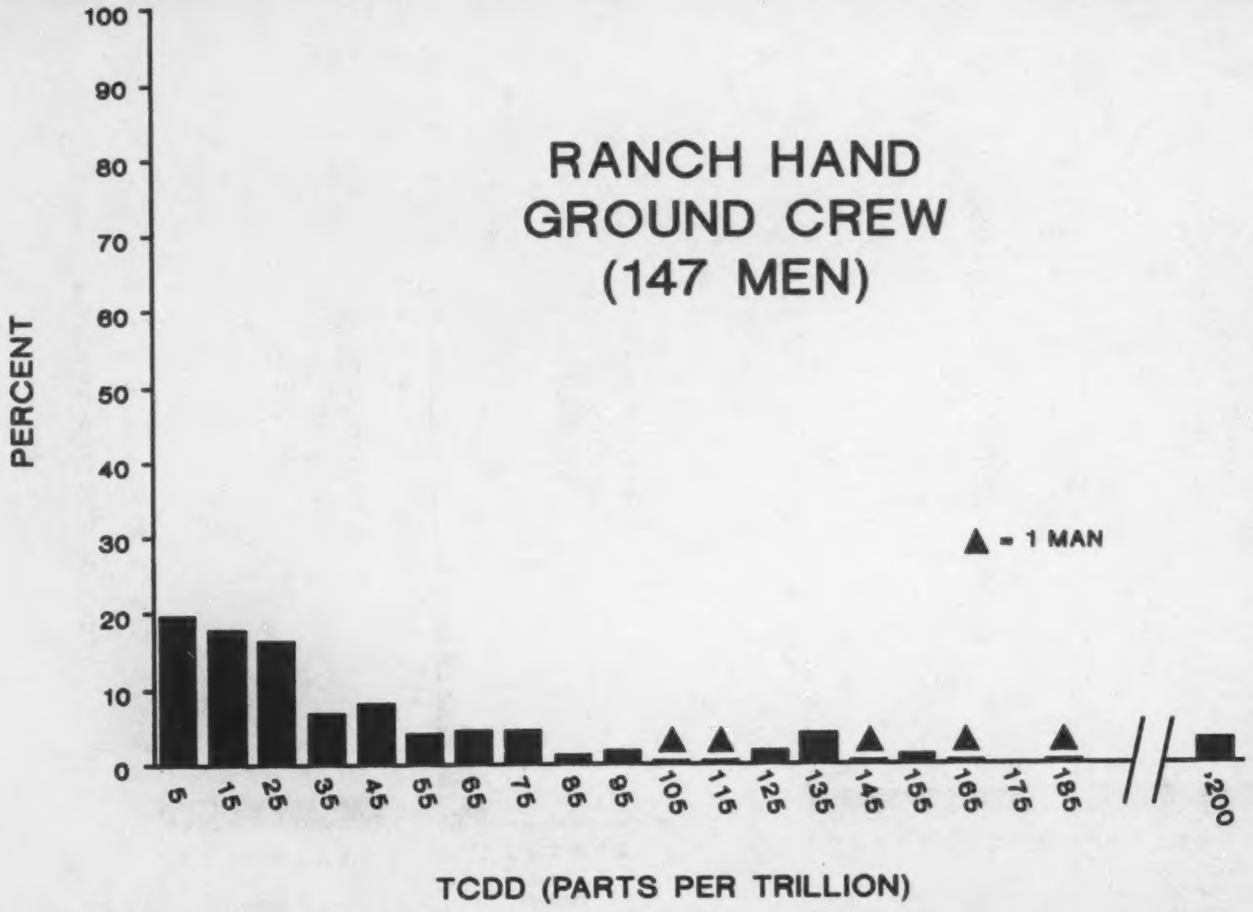


ATTACHMENT C



ATTACHMENT D

Random sample of 1-tour US Army soldiers discharged at E-1 to E-5 rank.

	Vietnam	Non-Vietnam
Interviewed	7,924	7,364
Examined	2,490	1,972
Semen Analysis	324	247

Social characteristics similar (education, employment, income, marital).

Psych. prevalence: (MMPI/DIS)

Significant differences (95% CI excludes 1.0)

Depression	4.5%	2.3%
Anxiety	4.9%	3.2%
Alcohol abuse	13.7%	9.2%
Ever had combat-related PTSD	14.7%	(not analyzed)
Had it during past month	2.2%	(" ")

Medical history: (Reported by veterans on interview--no diff. in cancers)

"Fair/poor" health	19.6%	11.1%	
Limited activity	26.6%	21.5%	
Prescribed medications	19.1%	16.8%	
Somatic symptoms	9.5%	5.7%	
Hypertension	25.4%	20.3%	(no diff. on exam)
Benign growths	19.0%	17.1%	
Chloracne	1.4%	0.3%	(no diff. on exam)
Other skin conditions	31.2%	19.7%	(no diff. on exam)
GI ulcers	12.5%	9.8%	
Hepatitis	4.8%	3.3%	
Other liver conditions	2.7%	1.8%	
Urinary problems	15.7%	13.7%	(no diff. on exam)
Fertility difficulties	20.0%	15.5%	
(Number of children after entry into Army	1.6	<-no diff.-> 1.6)	

Medical examinations: (Objective evidence--no diff. in immune system or in porphyria)

Low sperm concentration	15.9%	8.1%
Past hepatitis B infec.	14.1%	11.1%
Stool occult blood	1.3%	0.5%
High freq. hearing loss	14.4% / 18.4% R / L	9.9% / 12.9% R / L

Reported birth defects in children per 1000:	64.6	49.5	*
	<--different-->		|
Major/minor defects found in birth records per 1000:	60.9	57.8	|
	<-- no diff.-->		v

* Probable under-reporting of defects by non-Vietnam group.

DEPARTMENT OF THE AIR FORCE

HOUSE OF REPRESENTATIVES

SUBJECT: Agent Orange

STATEMENT OF: MAJOR GENERAL ALEXANDER M. SLOAN
Deputy Surgeon General
United States Air Force

8 June 1988

NOT FOR PUBLICATION UNTIL RELEASED
BY THE COMMITTEE ON VETERANS' AFFAIRS
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
HOUSE OF REPRESENTATIVES

Thank you for the opportunity to present an update on the progress of the Air Force Health Study of personnel exposed to herbicides in Southeast Asia.

In 1978, the United States Air Force responded to Congressional and veteran's interest in the Agent Orange issue and began work on an epidemiologic study of the possible health effects of exposure to herbicides and their 2,3,7,8-tetrachlorodibenzo-p-dioxin (referred to dioxin or TCDD) contaminants. Our study focused on Air Force veterans who served in the Ranch Hand defoliation operation during the Vietnam conflict.

In the interest of addressing the concerns of veterans, the Air Force Health Study (AFHS) was based on a scientific approach to the Agent Orange issue. The Air Force developed a protocol for a study including all 1267 members of the Ranch Hand unit serving from 1962 to 1971 and a group of matched comparisons. The comparison group was selected from the population of Air Force veterans who served in C-130 aircraft units stationed in Southeast Asia during the same time period. They were matched to the Ranch Hand group by age, race and job (pilot or copilot officer, officer navigator, non-flying officer, flying enlisted and ground enlisted). It was assumed that the comparisons were not exposed to herbicides or dioxin in Southeast Asia.

The protocol was subjected to extensive review by scientific peer groups including the University of Texas School of Public Health, the Air Force Scientific Advisory Board, the Armed Force Epidemiologic Board, the National Academy of Science and the Science Panel of the Agent Orange Working Group.

The protocol was approved in February 1981 and the first questionnaires were administered in October of that year. The baseline physical examinations were begun in January 1982 by a civilian contractor. Since that time, we have published four mortality reports and two morbidity reports. The study is a planned 20 year research effort.

What is the probability of this study to detect group differences? Power is the probability of detecting a group difference, usually expressed as a relative risk or a shift in mean values. This study has good power to detect relative risks of two or three when the disease rate in the comparison population is 5% or more. Similarly, the study has good power to detect a mean shift of 5% or more. For rarer diseases, our power is decreased. The power should improve with the passage of time since the basic disease rates should increase as the group ages.

A comprehensive clinical evaluation will be performed throughout the study with examinations by internal medicine, neurology and dermatology specialists. Psychological and laboratory testing will also be included. Participation in the study has been excellent with 87% of the invited Ranch Hands and 75% of the invited comparisons taking part in the initial evaluation; 93% of those who participated in the initial study have returned for the follow-up evaluations.

The Morbidity Report published in October 1987 found that there were some differences in subjective measures of general health in the enlisted ground personnel, but these findings were not confirmed by more objective measurements. On balance, the assessment of general health did not reveal any reason for concern in this clinical area.

No significant differences between the Ranch Hand and the comparison groups were seen in the 1987 report for skin or systemic cancers. However, when overall lifetime basal cell carcinoma rates were adjusted for risk factors involved in the cause of such cancers (e.g. geographic area of residence, skin color, skin reaction to sun) Ranch Hands had a statistically significant higher number of basal cell carcinomas than the comparisons. This type of skin cancer is the most common neoplasm in the white population in the United States, is not prone to distant spread and is usually rapidly cured with simple treatment. These cancers were found in sun exposed areas of the body.

There were no unadjusted group differences for systemic lifetime cancer in the 1987 report. However, when occupation was considered, there was a significant increase among the Ranch Hand enlisted flyers for systemic cancer. These results may be unstable since they are based on only 5 cases of cancer and even one or two additional cases would alter these findings, which do not correlate with our estimated exposure index. These men are not in the group that we think had the heaviest exposure to the herbicides in Southeast Asia. A better understanding of the relevance of this observation must await the results of the serum dioxin testing.

During the interval between the two evaluations, a single case of soft tissue sarcoma and one case of non-Hodgkins lymphoma occurred in the Ranch Hand group. Earlier similar cases were found in the comparison group. This makes the incidence of these two conditions equal in both groups.

The neurologic assessment of cranial nerve function, peripheral nerve function and central nervous system coordination, did not reveal any consistently significant group differences in the 1987 report, although abnormalities tended to aggregate in the Ranch Hands. The Babinski reflex (found adverse in the Ranch Hands at the 1982 Baseline examination) was equal in both groups at follow-up. Age, alcohol and diabetes showed classical effects with many neurological measures.

Extensive psychological testing was conducted. In general, while statistically significant differences in some portions of the testing were seen, they were quite variable in nature and their clinical relevance is unknown. Post traumatic stress disorder was evaluated and only 1% in either group had this condition. There were no group differences for current or past neuroses or psychoses. Age, educational level, and alcohol history showed strong and expected effects on the psychological measures.

Both the interval and lifetime history of liver disease were equal in both groups, as was a lifetime history of peptic ulcer disease in the 1987 report. Of the 11 laboratory tests performed to evaluate liver function, only two showed significant differences in the average values in the Ranch Hand and Comparison groups. However, the number of men who had abnormally high levels was not different in the two groups. The uroporphyrin test, which is the best indicator of porphyria cutanea tarda, was normal in the Ranch Hands. The comparisons had significantly higher levels of uroporphyrin, but this is considered to be of no clinical relevance.

In the 1987 dermatological assessment, not one case of chloracne was diagnosed on examination, nor was historical acne anatomically distributed in a pattern that suggested past chloracne in the Ranch Hand group. Exposure and comparison with the results of the 1984 report were also unremarkable.

The 1987 cardiovascular evaluation showed that when heart disease of all types was considered, the frequency of disease reached statistical significance. However, there were no group differences for hypertension or heart attacks, the types of heart disease we worry about the most. Other assessments of cardiac function by blood pressure measurements and electrocardiogram did not reveal any meaningful group differences.

Evaluation of peripheral pulses by the more accurate Doppler technique revealed group equivalence in marked contrast to the Baseline examination, which found significant pulse deficits in the Ranch Hands by manual measurement. As well, the effect of tobacco was controlled by restricting smoking for four hours prior to the measurement of the pulses. Overall, the groups were remarkably similar in cardiovascular health.

The 1987 assessment of eight hematological measures showed no significant group differences. In fact, the groups were more similar at the follow-up examination than at the Baseline examination. Age, race, and smoking were significant risk factors for most hematological measures.

The groups did not differ significantly in reported kidney disease, in the 1987 report, although the Baseline questionnaire noted such in the Ranch Hands. Five laboratory measures of renal function were similar between groups in the unadjusted analyses. No pattern of results suggested a detriment to either group in the adjusted analyses.

For endocrine function, TSH and testosterone means were significantly higher in the Ranch Hands, in the 1987 report, but these results were within the normal range. Impaired glucose tolerance tests revealed an excess in the comparison group. Examination results for past thyroid disease, thyroid and testicular abnormalities, and additional tests for cortisol level and T3 % uptake were similar in both groups. Age, race, occupation, percent body fat, and personality type were taken into account as pertinent variables. Overall, the endocrine health status was comparable in both groups.

Comprehensive immunological tests, composed of six cell surface marker studies and three functional stimulation studies showed no significant group differences in the unadjusted analyses. Age, smoking, and alcohol usage were accounted for in the analysis. The assessment of delayed hypersensitivity by skin testing was declared invalid because of excessive reader variation and shifting diagnostic criteria.

The pulmonary assessment, in the 1987 report, consisting of past history, physical examination, and x-ray results did not indicate any consistently different disease patterns in the two groups. Age and lifetime smoking history were important risk factors for most pulmonary measures.

The exposure index analyses, which were stratified by occupation, revealed sporadic differences between exposure levels; however, there were no consistent dose-response relationships that supported an herbicide effect for any clinical area.

Comparisons between the 1984 study and the 1987 findings were conducted for 19 variables, and 5 showed significant differences in the changes of the groups between the Baseline and follow-up examinations. Of these 5 variables, one (sedimentation rate) was believed to be related to a change in laboratory methods, and the other four (Babinski reflex, depression, platelet count, and manual all pulse index) were attributed to true changes over time for the groups. In comparing all results between the examinations as well as the formal longitudinal analyses, we see a subtle, but consistent decrease in group differences over the three year period.

In summary, the 1987 morbidity report concludes that there is insufficient evidence to support a cause and effect relationship between herbicide exposure and adverse health in the Ranch Hand group at this time. The study has revealed a number of minor medical findings that require continued surveillance. In full context, the results of this study are encouraging evidence that, at this time, the current state of health of the Ranch Hand participants appears unrelated to herbicide exposure in Southeast Asia. However, we still cannot exonerate the herbicide at this time.

In addition to the morbidity analyses, periodic evaluations of the death (mortality) experience of the Ranch Hand and comparison groups have been conducted and reported. Analyses have been directed at total and cause-specific death rates with adjustment for year of birth, race, rank and occupation. All reports have contrasted survival of all known Ranch Hands who had not died in combat while in Vietnam, 1257, with 6171 matched comparisons. As of December 31, 1984, the overall mortality of the Ranch Hand group (4.4%) was nearly identical to that of the comparison group (4.6%). Ranch Hand officers have experienced fewer deaths than comparison officers while more Ranch Hand enlisted personnel have died than their matched comparison, but none of these differences are significant. As of December 31, 1985, the overall Ranch Hand and comparison mortality were 4.7% and 5.1% respectively. Due to the small number of deaths that occurred during 1985, an abbreviated mortality report was published in 1986. The 1988 mortality update is currently underway and is expected to be published this summer. This analysis will include the death experience of 20,000 men (all of the Ranch Hands and all men assigned to C-130 aircraft units in Southeast Asia between 1962 and 1971.)

Recently published follow-up evaluation of the 1984 baseline morbidity report (United States Air Force Personnel and Exposure to Herbicide Orange by Richard Albanese, M.D.) evaluates the relationship between the findings of the 1984 study and a literature review of the toxicology of dioxin. The results of subsequent follow-up clinical examinations, released in October 1987, were not included in this reevaluation. Variables from 11 clinical areas were selectively evaluated in the report: weight loss, malignant disease, birth defects, neurological disease, psychological problems, liver diseases, the presence of chloracne, heart disease, immunological function, endocrine status and death. The review highlighted six clinical areas warranting more in-depth evaluation in the future. Although this report used another approach to analyzing the 1984 data, the conclusions were essentially the same as in previous reports. We can neither definitely establish nor refute a link between dioxin and disease.

There has been much controversy concerning the relationship between herbicide exposure and birth defects in children. Initial evaluation of fertility and reproductive systems found there was a significant disparity between groups for reported birth defects. We incorrectly concluded that group differences were confined to minor skin conditions. The baseline findings of overall group differences in reported birth defects is being reinvestigated with full medical record verification of the birth defects reported on all children fathered by study participants. Over 6,000 medical records are under review. We expect to complete this analysis next summer.

Exposure Index

The initial study protocol developed an estimated exposure index that reflects the best calculation of the effective number of gallons of herbicide to which the airmen was exposed. It is based on an estimate of gallons of herbicide sprayed per month (1962-1971), the levels of dioxin contamination and the number of men assigned each month.

Individual exposure measurements could not be made. While the method used to establish the exposure index was state-of-the-art, several assumptions concerning individual work habits and circumstances had to be made.

In mid 1986, strong evidence was demonstrated by the Centers for Disease Control (CDC) and other institutions that dioxin levels could be measured in blood as well as fat tissue. The CDC demonstrated that blood levels and fat tissue appear to be equivalent. The Air Force recently concluded a collaborative study with the CDC to validate the study and estimate the half-life of dioxin in humans. This pilot study of 200 serum samples confirms clear and meaningful dioxin exposure did occur in the Ranch Hand group. The range of dioxin exposure in the Ranch Hand group (3-314 parts per trillion) is significantly higher than the control group (3-21.3 parts per trillion). A part per trillion is equivalent to one second in 32,000 years.

The distribution of dioxin levels for Ranch Hands confirms our belief that many members of this group had significant exposure to dioxin as compared to the general U.S. population and our comparison group. The serum dioxin measurement will quantify actual dioxin body burden and provides an individual exposure assessment.

The ability to improve the estimated exposure index with the serum dioxin test is a major opportunity in the scientific evaluation of the Agent Orange issue. This new serum dioxin assay will provide an accurate measure of the current body burden of dioxin. It should also be possible to estimate the half-life of dioxin in humans. Initial calculations indicate that the dioxin half-life in humans is approximately 7 years. Serum has been collected and stored from 2,010 study participants.

Within the next two years another morbidity report on the 1987 examination results, mortality reports and an expanded birth defects analysis will be completed.

We have analyzed the results of the first 5 years of our 20 year research study looking at the herbicide health question. Nearly 100 government, academic and industry scientists have guided and contributed to the study since its inception.

Our studies have not been able to establish a definitive adverse cause-effect relationship between adverse health and Herbicide Orange exposure. However, our studies identified some issues that require further evaluation.

The Air Force Health Study is the premier federally funded herbicide-related study underway. Its findings are important to our veterans and to their families. With your continued support, our work will continue. I will be happy to answer any questions at this time.

TESTIMONY OF DR. MICHAEL GOCHFELD ON RESEARCH RELATED TO VETERAN EXPOSURE TO HERBICIDES.

JUNE 8, 1988

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My testimony today covers the following areas:

1) Brief remarks on dioxin and Agent Orange exposure
2) New Jersey's Pointman Project
3) Blood Dioxin as an Indicator of Past Exposure
4) Half life of Dioxin in the Human Body
5) Conclusion from Pointman I and Progress of Pointman II
6) Health of Veterans
7) Suggestion for a Tissue Archive
8) Conclusion on Veterans' Status
9) Health Effects Studies
10) Critiques of Studies
11) Interviews and Bias
12) Future Studies of Herbicide Exposure
13) General Lessons from Dioxin

BRIEF REMARKS ON DIOXIN AND AGENT ORANGE EXPOSURE

There is substantial controversy regarding the extent to which Viet Nam veterans were exposed to dioxin-contaminated herbicides and the extent to which such exposure may have jeopardized their health. There are some facts regarding dioxin exposure. As popularly used the term "dioxin" refers to a specific compound known to scientists as 2,3,7,8-tetrachlorodibenzodioxin or 2,3,7,8-TCDD. This is only one of many chlorinated dioxins, but it has two important features.

1) It is the most toxic of all the dioxins.
2) Because of its structure, it and it alone, was produced (unintentionally as a contaminant) in the manufacture of the herbicide 2,4,5-T. which comprised half of Agent Orange.

The attached figure from an article recently completed for a medical journal, illustrates this point.

2,3,7,8-TCDD which we will from now on refer to as "dioxin" is highly toxic, particularly in guinea pigs. It is not quite so toxic in the rat or mouse. No one is quite sure how sensitive humans are because there are so few cases of known human exposure to TCDD. It seems clear that the human is not exquisitely sensitive to dioxin. But no study has offered compelling evidence regarding just how sensitive humans are. It is not appropriate to disregard dioxin, and in fact recent research suggests that we will soon be able to identify a dioxin syndrome.

There are writers who believe that the evidence of its toxicity in humans is so slight that there is no reason to either fear or study dioxin. On the other hand there are many who, in consideration of its extremely high toxicity in animals, feel that complacency is not warranted. Many Viet Nam veterans fall in the latter group, a group that feels that high quality biomedical studies of dioxin exposure should be conducted.

I do not have unique insight into dioxin's human toxicity, but I see no reason why such studies should not be undertaken. The National Institute of Occupational Safety and Health is conducting one such study. The Air Force is conducting another. CDC has recently argued that it is not feasible to conduct such a study because of the difficulty in determining exposure. Our current research addresses that issue.

NEW JERSEY'S POINTMAN PROJECT

Faced with arguments that such research should not or cannot be done, the New Jersey Agent Orange Commission has responded with a research approach which demonstrates that appropriate study of veterans is feasible. Our research, known to veterans as the Pointman Project, is continuing today. The results of phase I were published in March 1988 in the Journal of the American Medical Association. This article is attached, and I will summarize its highlights.

A. Methods: We identified 10 persons with a known history of high level exposure to Agent Orange in Viet Nam. For each of these we selected a matched control who had also served in Viet Nam, but had no known herbicide exposure (Viet Nam controls). We also sought a matched control who had served in the military at the same time but had not gone to Viet Nam. We only found seven suitable "era" controls.

Each of the 27 persons underwent a three day inpatient medical evaluation which included the drawing of a large (350 ml) blood sample and a fat biopsy which were used to analyze for 13 dibenzodioxin and dibenzofuran compounds, including 2,3,7,8-TCDD. The JAMA paper reports the results of the blood and fat analyses for these thirteen compounds.

B. We found a very strong correlation between dioxin levels in blood and fat. This was very reassuring since it will allow future researchers to use blood only, thereby avoiding the need to obtain fat biopsies. Moreover we demonstrated that there was no appreciable benefit to be gained by a 24 hour fast compared with a long-overnight (14 hour) fast. These two accomplishments make it quite feasible to use blood dioxin levels as an indicator of past exposure.

C. The crux of the study however was the comparison of dioxin levels in the exposed vets versus the controls. We compared blood and fat dioxin levels for each vet against the levels in his matched Viet Nam control. In 9 of 10 pairs the exposed vet had the higher dioxin level in fat and in 6 of 9 pairs (one pair was excluded because of laboratory mishap) the exposed vet had the higher dioxin level in blood. The former difference is highly significant statistically; the difference for blood is marginally significant. This means that if there were no real difference in dioxin levels in veterans who handled Agent Orange versus those who didn't the chance that we would get the differences we found, are very small; less than 1 in 100 for the fat data. Thus anyone can be confident that exposed veterans did indeed have exposure, did get dioxin in their bodies, and even 15-20 years later, have higher dioxin levels than their counterparts who did not have exposure.

D. Comparing the Viet Nam controls with the era controls, we found that both had about 5 parts per trillion of dioxin in their fat. This is approximately the same level that has been found in the population at large in industrialized countries. We can assume therefore that all of us are probably close to a background level of 5 parts per trillion. The highest value observed in any of the controls was 14.7 ppt. But some of the exposed veterans had over 100 parts per trillion, and the average value was above 40 parts per trillion. Three exposed veterans had levels below 10 ppt. Two of these had occupational histories which indicated that they really had low exposure, but although this explains why they may be low today, we keep them in our "exposed" group. We thus suggest using a cutoff of 15 ppt. A veteran who has above 15 ppt has a high likelihood of having been exposed. One who has below 15 ppt still has a 30% chance of having been exposed, but this is probably acceptable misclassification.

E. For those who might be skeptical because of our choice of a small sample size (10 exposed men and their 17 controls), it is essential to recognize that there were 13 dioxin and furan compounds detected, any one of which might have been high or low in the exposed vets. Of these, only 2,3,7,8-TCDD (the one which was the contaminant in Agent Orange) was significantly higher in the exposed men.

BLOOD DIOXIN AS AN INDICATOR OF PAST EXPOSURE

Based on these results we see no reason why a substantial epidemiologic study could not be conducted. The blood dioxin level would be sufficient to classify the veterans into an exposed or non-exposed status.

One approach would be to randomly select 1000 veterans, measure the dioxin in the blood and classify them into three groups. The upper third could be selected as an exposed group, the lower third as a control group.

To be sure the matter is more complicated. Given the same exposure, two veterans side-by-side might have had different uptake of the herbicide and therefore gotten different mounts in their body. Moreover, no two people are exactly the same in how they metabolize dioxin. So two people who had the same uptake 20 years ago, might have different levels today.

However, with a large sample size such variability can be taken into account.

HALF LIFE OF DIOXIN IN THE HUMAN BODY

Foreign compounds that enter the body leave it at a certain rate. That rate can be expressed as a half life, the time required for half of the substance to leave the body (assuming that exposure has not continued). The half life of dioxin is not known with certainty. Based on recent research by the CDC the half life is at least seven years, and I suspect that it is probably between 7 and 10 years. That is the average person will clear half of the dioxin from their system in 10 years. Then half of the remaining will be cleared in the next ten years, etc.

Knowledge of the half life is important if one is to estimate the magnitude of exposure or the level of dioxin in the body at the time exposure occurred 20 years ago.

Thus if we take a seven year half life, our veteran with 180 ppt in 1985, would have had about 360 ppt in 1978 and about 720 ppt in 1971, a time when herbicide use was terminated.

CONCLUSION FROM POINTMAN I and PROGRESS OF POINTMAN II

We think that we have shown evidence that herbicide handlers have significantly higher levels of dioxin in their bodies than unexposed Viet Nam veterans. Studies conducted by the Air Force and by CDC appear to confirm this finding. It is not surprising that herbicide handlers had exposure, but some people are surprised that we can still find evidence of that exposure 20 years after the fact.

The next step is to answer the question whether the "average" combat veteran had significant exposure as reflected by higher than background levels in their bodies today. This is the quest of the Pointman II project. We have selected three groups of combat veterans with a reasonable likelihood of exposure. These represent men from a batallion that operated for many months in the midst of an area that was subject to frequent defoliation, it includes marines who were in the field for months in defoliated areas, and it includes the crew of the river boats which operated along the waterways in areas where the vegetation on the banks had been cleared by defoliants.

The results of this study will help determine whether herbicide exposure was indeed limited to spray handlers or whether it may have been the fate of a large number of veterans.

HEALTH OF VETERANS

There is much written about the fate and plight of the Viet Nam veterans. They returned from an unpopular war to an unsupportive society that was just phasing out the activism of the 60's. The vast majority went to school or work, returned to families, and resurrected their lives with no insurmountable problems, but the caricature that emerged was of veterans who never adjusted, who used drugs, were unemployed, could not sustain relationships, were subject to fits of violence, were angry and maimed and suffered devastating flashbacks. Some veterans indeed fit this pattern and others were victimized by the caricature itself.

Initial explanations had to do with the unique culture of the Viet Nam war, so different from the wars we had fought before. Then we learned about PTSD, a formal psychiatric syndrome, by no means new. More recently some have argued that the psychologic effects may actually represent toxic manifestations of herbicide exposure itself. I think this is one question that needs to be addressed. Although I will be surprised if there is a clear psychotoxic effect from herbicide exposure, I have no doubt that the fear of having been poisoned is sufficient to have far-reaching psychopathologic consequences. We have seen this in many non-veterans who homes or offices are suspected of being contaminated. Our Pointman projects include psychologic and psychiatric evaluations, but this is a miniscule sample, fewer than 100 people when we are done.

TISSUE ARCHIVE

One of the important ways in which the Veteran community can be helped would be to set up a tissue archive system. Surgical or autopsy specimens could be preserved, much as in a library, for future analysis when new techniques or new ideas become available. Such archives exist in other areas of medicine and pathology. Such an archive allowed scientists to determine the Legionnaire's Disease was not a new disease, for antibodies were found in blood specimens obtained years before the Philadelphia outbreak. Ideally the Armed Forces Institute of Pathology is a logical place for such an archive, but given the political climate surrounding veterans and Agent Orange, I regrettably suggest that such an Archive be established elsewhere, probably in a non-profit network established specifically for that purpose.

The startup costs for an archive are not large, probably on the order of $100,000, but it is essential to adequately maintain the facility, something which will probably require about $50,000 per year in personnel, electricity, and other operating expenses.

CONCLUSION ON VETERANS STATUS

Like any other subgroup there are members of the Viet Nam veterans community who have significant social, psychosocial, and/or physical problems. Many of the questions regarding the relationship of their health status to their "tour" of Viet Nam or to exposures that occurred there.

others have no doubt that their health problems are directly attributable to dioxin exposure. I suspect that to a great extent their certainty is enhanced by the government's steadfast refusal to recognize the possibility that Agent Orange exposure harmed American veterans. It is a clear case of "I fear thou dost protest too much". Certainly if the government had undertaken to get to the bottom of the exposure problem 15 years ago in a scientifically sound and humane fashion, much of the concern would have long since resolved.

Recognition of the persistent health and/or social problems of veterans does not require sophisticated scientific research. Humane application of biomedical and social service skills can be applied to solve individual problems regardless of what long-ago contributed to or caused the problem, and regardless of the pet theories of the veteran or the VA regarding his/her individual problem.

HEALTH EFFECTS STUDIES

The Pointman Project includes detailed medical and psychological evaluation of the participants. The information is made available to them and they are counselled regarding any necessary professional care. However, the Pointman project is not primarily a health effects study. In fact, the selection process specifically excluded individuals who had evidence of a "dioxin syndrome" or who were otherwise seriously ill. Many enthusiastic volunteers fell into these categories and lamentably could not participate in Pointman. Some of these individuals were evaluated outside of the research protocol in order to provide them guidance.

We thus bent over backward to provide a negative bias to our study by omitting those individuals who might have been the most likely to have significant effects.

CRITIQUES OF STUDIES

I think there remains a real need to study the health of Viet Nam veterans, including a focus on dioxin. I do not know how large the group of exposed veterans is. We can all agree that herbicide handlers represent a high risk group, but what about the average foot soldier, the person who actually participated in military operations on the ground.

At any one time only about 1 of every 9 servicemen in Viet Nam was involved in combat. In the course of a year, the average figures are probably about 1 in 4 or 1 in 5. Thus only 20-25% of the veterans were involved in operations, and of these only a fraction, perhaps one quarter, were afield in areas treated with herbicides. Given 2.5 million Viet Nam veterans this still amounts to 150,000 dioxin exposed veterans. On the one hand this is still a significant group. On the other hand, any study which appears to evaluate the health status of veterans by focusing on all Viet Nam veterans clearly cannot provide any insight into the status of the exposed veterans since their numbers are severely diluted by including the much larger number of unexposed individuals.

The paucity of studies on Viet Nam veterans is gradually changing. In addition to the New Jersey study Jeanne Stellman, PhD and Steven Stellman, PhD have completed some extensive studies of veterans, and when there results are published they will document a variety of statistically significant health effects. I have read with interest several studies recently published by the Centers for Disease Control.

These have been completed by the Centers for Disease Control Vietnam Experience Study. The Viet Nam Experience study specifically did not focus on exposure to herbicides. The study appears to exclude career men, including only those who served only one term of enlistement. The papers published from this study in the Journal of the American Medical Association include the following:

Postservice mortality among Vietnam Veterans. JAMA 257:790-795, 1987.

Health Status of Vietnam Veterans
I. Psychosocial Characteristics. JAMA 259:2701-2707, 1988
II. Physical Health JAMA 259:2708-2714, 1988
III. Reproductive Outcomes and Child Health. JAMA 259:2715-2719, 1988

These papers report on a "multidimensional assessment of the health of Vietnam veterans". This was mandated by the Congress under the Veterans Health programs Extension and Improvement Act of 1979. The article starts out identifying the problem: "Many veterans are concerned that military service in Vietnam may have adversely affected their health and perhaps that of their children." They used a random sample of enlisted men who entered the army between 1965 and 1971. This yielded 7924 Viet Nam and 7364 non-Viet Nam veterans. These were interviewed by telephone. Subsequently 2490 Viet Nam veterans and 1972 non-VN vets underwent a comprehensive medical and psychological examination.

The two groups were demographically similar in terms of education, employment, income, marital status and satisfaction with personal relationships. This is of interest to me since I had the distinct impression that soldiers who ended up in Viet Nam were not a random subset of the military, but represented an excess of minorities, for example. Closer look at Table 2 indicates that 14% of the Viet Nam vets had not completed high school compared with 11.6% of the non-VN vets and only 17.8% were college grads compared with 21.7% of the non-VN Vets. Thus the educational status was not similar. The non-vets were more likely to be professional and less likely to be unemployed.

There were some significant differences between the two groups:

	Viet Nam	non-Viet Nam
Depression	4.5%	2.3%
Anxiety	4.9%	3.2%
Alcohol abuse/depend	13.7%	9.2%

One of the most important features of Viet Nam service is the condition labelled Post-traumatic Stress Disorder. The CDC study reported that an amzazingly high proportion, nearly half, of the veterans experienced at least one symptom related to PTSD while 15% met the diagnostic criteria for combat-related PTSD at some time. Even more significant, in the month preceeding the interview, 21% of the interviewees had experienced PTSD symptoms, and 2.2% currently suffered full-blown PTSD. Veterans with PTSD were significantly more likely to experience substance abuse and/or depression or anxiety.

The study provided some comforting data. Viet Nam veterans were not more likely to be in jail or to be handicapped. Moreover, marital status and proportion divorced did not differ among the two groups.

As might be anticipated the risk factors for poor psychological status among the veterans included 1) Viet Nam service, 2) non-white, 3) less than 19 years old at enlistment, 4) low technical test scores at enlistment. Thus young, less well-trained, non-white Viet Nam veterans represent a high risk group for psychological problems. This is no surprise, but the CDC study has provided important validation of this factor.

II. The health effects study showed that during the telephone interview the Viet Nam veterans were more likely to report health problems than those who hadn't served in Viet Nam. The problems reported in excess included 1) poor health status (19.6%), limitation of activities (26.6%), high blood pressure (25%), chloracne (1.4%), and other skin conditions (31.2%). At the time of the examination, the history obtained by the medical examiners, revealed a similar discrepancy. There were still twice as many vets who believed they were in poor health, and nearly twice as many reported physical symptoms. There was the same excess in high blood pressure, and a 50% excess in cancer, and a 6-fold increase in chloracne. There excess in skin conditions was the same, and in fact the health history on examination closely paralleled the telephone interview results.

The article reports that the examining physicians did not know whether a veteran had been to Viet Nam or not. Dermatologic examination did not find an excess of chloracne or indeed, any other skin condition. If this is a generally true finding, that Viet Nam veterans do not have an excess of skin conditions or chloracne, then the consistent self-report excess reflects a significant psychomedical problem. A great excess of veterans believe that they are ill and believe that they have skin problems. Objective findings reveal that significantly more Viet Nam veterans experience high frequency hearing loss, not very surprising. Neurobehavioral performance did not differ.

In fact most of the tests show relatively little difference among the two groups. However, if one looks closely at the blood tests for example, one finds that of the 13 tests, the percent of men outside the normal range was greater for Viet Nam vets in eight cases and lower in only two cases (three tests had a tie percentage). This discrepancy would not be expected by chance alone.

Semen analyses were performed on 324 Viet Nam veterans and 247 non-VN vets. Twice as many Viet Nam vets had low sperm counts, and the percent with non-motile sperm or abnormal sperm was also greater than for non-VN vets. The CDC evaluated this more closely and could not connect the semen abnoralities with particular subsets of veterans. The CDC did not find that the abnormalities were related to self-reports of herbicide exposure.

The reproductive study has a similar outcome. Significantly more Viet Nam vets reported adverse reproductive outcomes, but the objective analysis indicated that children of VN vets did not appear to be at greater risk of birth defects.

The 7924 Viet Nam vets reported 15,009 pregnancies (1.89/person), of which there were 12,788 births (85% of pregnancies), and 12,659 live births (98.9% of births). The comparable figures for the non-VN vets was 13,715 pregnancies for 7364 men (1.86/man), with 11,910 births (87% of pregnancies), and 11,777 live births (98.8%).

The interview study reported 64.6 anomalies per 1000 births to VN vets, compared with 49.5/1000 births for non-VN vets, a significant difference. Most of these were musculoskeletal defects. The birth records also noted an excess of major defects for the VN vets (28.5/1000 versus 23.5/1000), but this is not statistically signficant. Whether it is medically significant remains for discussion.

INTERVIEWS AND BIAS

One of the commonest problems with epidemiologic studies is recall bias. A person who has a problem is much more likely to recall all sorts of details than a "normal" person. A group such as Viet Nam veterans which has become highly sensitized over the past 20 years is certainly more likely to recall such things as birth defects, or to ascribe significance to events which others might consider trivial. Thus even though a medical encounter may place great weight on interview results, epidemiologists are rightfully wary of such reports. However, one approach to validate the reports of the Veterans would be to see their own medical records and to track down the birth records of their children to see whether the interview results are indeed biased.

Recall bias is particularly important for relatively trivial events (for example a miscarriage early in pregnancy or the use of a particular medication). There are certain events, however, which are so staggering, that no one is likely to overlook them. The diagnosis of leukemia in a child is clearly in this category, hence the excess of 12 cases among VN veteran children versus 7 among non-VN vets should be examined, even though the difference was not statistically significant.

The CDC researchers made a conscientious effort to identify subgroups of veterans who might be at excess risk. However, I note that even with the relatively large numbers, the study cannot easily identify subtle differences. The studies do indicate that on the whole the Viet Nam veterans do not have very much higher risk for various physical and reproductive outcomes than their non-VN counterparts. Whether there are subtle difference cannot be eliminated. Moreover, there may be specific high-risk subgroups among the VN veterans, and their status is inevitably diluted when they are part of a much larger population of low-risk VN veterans.

I have this same criticism of all of the studies which look at VN veterans as a whole. Most people who went to Viet Nam did not experience combat, suffered boredom and inconvenience more than fear and returned home to assume satisfying jobs and relationships. Diluting the significant minority who do not fit this category, makes it difficult to detect their problems.

I thus conclude that the CDC studies are extremely valuable and interesting, provide some reassurance for the entire veteran populations, and focus attention on identifying high risk subgroups. There are enough suspicions in these studies to warrant an open mind. Moreover, the physician in me, trained to listen and take a detailed history, rebels at dismissing self-reports, although the epidemiologist in me urges caution. An interview, after all, is how we find out about a person's health, and this applies to veterans as to anyone else.

FUTURE STUDIES OF HERBICIDE EXPOSURE

I must respectfully conclude by disagreeing with scientists who say it is impossible to do a sound study of the epidemiology of dioxin exposure. It may be difficult, but it is not impossible. Our research, and in fact the CDC's own research, on blood levels of dioxin provide a ready means of identifying exposed populations. The rationale for performing the study lies in the fact that there remain bountiful unanswered questions, particularly in the minds of the veterans, but in the minds of many scientists as well.

If the government chooses not to do definitive research, then it should fund a series of smaller scale, investigator-initiated, peer-reviewed research projects conducted by biomedical scientists around the country. These smaller projects would be able to clarify some of the exposure and health effects issues.

GENERAL LESSONS FROM DIOXIN

In addition to the veteran community dioxin several communities around herbicide manufacturing facilities or where waste oil has been used for dust control have experience contamination, and of course there is substantial interest in dioxins as an unwanted byproduct of incinerators. More than veterans anxiously await the improved understanding of dioxins.

I think there is another important lesson to be learned from the dioxin/Agent Orange story.

It is lamentable that so many of the complex issues surrounding toxicity of substances to humans is further confused by the inevitably strong vested interests. We have seen this in the case of vinyl chloride, a carcinogen whose regulation by the federal government was bitterly contested as unwarranted and impossible by the chemical industry. When regulation prevailed, industry quietly set about the task of complying, and the "impossible" was quickly seen to be not only feasible, but lucrative as well. The outcome of regulating vinyl chloride has been the virtually complete elimination of angiosarcoma of the liver, despite the fact that some scientists argued that the evidence regarding angiosarcoma and vinyl chloride was weak.

In the case of dioxin both the Federal government and the chemical industry have ignored or pooh-poohed the health risks, despite a wealth of laboratory data. Coupled with inconsistent activities such as the 'buy-out' of Times Beach, Missouri, veterans and the public can only form overwhelming distrust of the nay-sayers. Thus even if dioxin exposure in general, and Agent Orange exposure in particular, were indeed innocuous, there are those who would never believe it, because the performance of the researchers has completely convinced them that there must be a cover-up.

This should never happen again. The reluctance of a government and its regulatory agencies to regulate, even in the face of persuasive evidence of harm, in the long run does no one a favor. The public continues to be injured, and conscientious companies that do clean up and control exposures, suffer the unfair competition of those that do not.

I am not, by nature, a chemophobe. I do not have to be convinced that many chemicals have served mankind well. I happen to believe that with proper controls, protective equipment, and education, even highly toxic materials can be used safely, and we use such chemicals in our laboratory. However, conversely I also believe that there is no chemical so safe that some "damn fool" can't figure out a way of handling it dangerously. Unfortunately the evidence indicates that uncontrolled use of herbicides, despite their low human toxicity, falls into the latter category.

In addition, to urging the Federal government reverse its not-so-benign neglect of dioxin, I would like to see the resurrection of conscientious regulation by Federal agencies such as the Environmental Protection Agency, the Occupational Safety and Health Administration, the Consumer Product Safety Commission, the National Toxicology Program. At the very least the laws we have need to be implemented with less regard for special interests. They are not very strong laws, but we can ill afford to continue to ignore them.

ATTACHMENTS:

1. Kahn et al. DIOXINS AND DIBENZOFURANS IN BLOOD AND ADIPOSE TISSUE OF AGENT ORANGE-EXPOSED VIETNAM VETERANS AND MATCHED CONTROLS. Article published in Journal of American Medical Association, March 18, 1988.

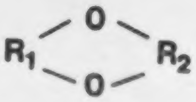
2. The Measurement of Dioxin Levels in Viet Nam Veterans who were heavily exposed to Agent Orange during the war: a pilot project. [Lay Language Description] from the New Jersey Agent Orange Commission for the Pointman Project

3. Gochfeld et al. DIOXIN EXPOSURE AND HEALTH: NEW ADVANCES AND OLD CONTROVERIES. Article in press in New Jersey Medicine.

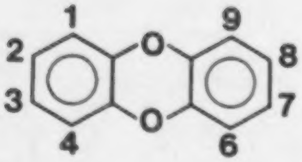
ILLUSTRATIONS OF DIFFERENT KINDS OF DIOXIN COMPOUNDS

R=a miscellaneous organic substance

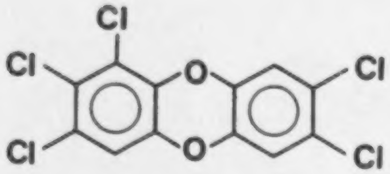
a) a dioxin



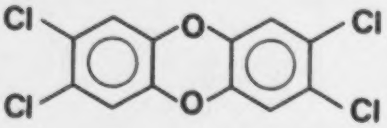
b) dibenzodioxin


1
9
2
8
3
7
4
6
O
O

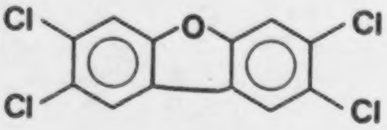
c) 1,2,3,7,8 PCDD


Cl
Cl
Cl
Cl
Cl
O
O

d) 2,3,7,8 TCDD

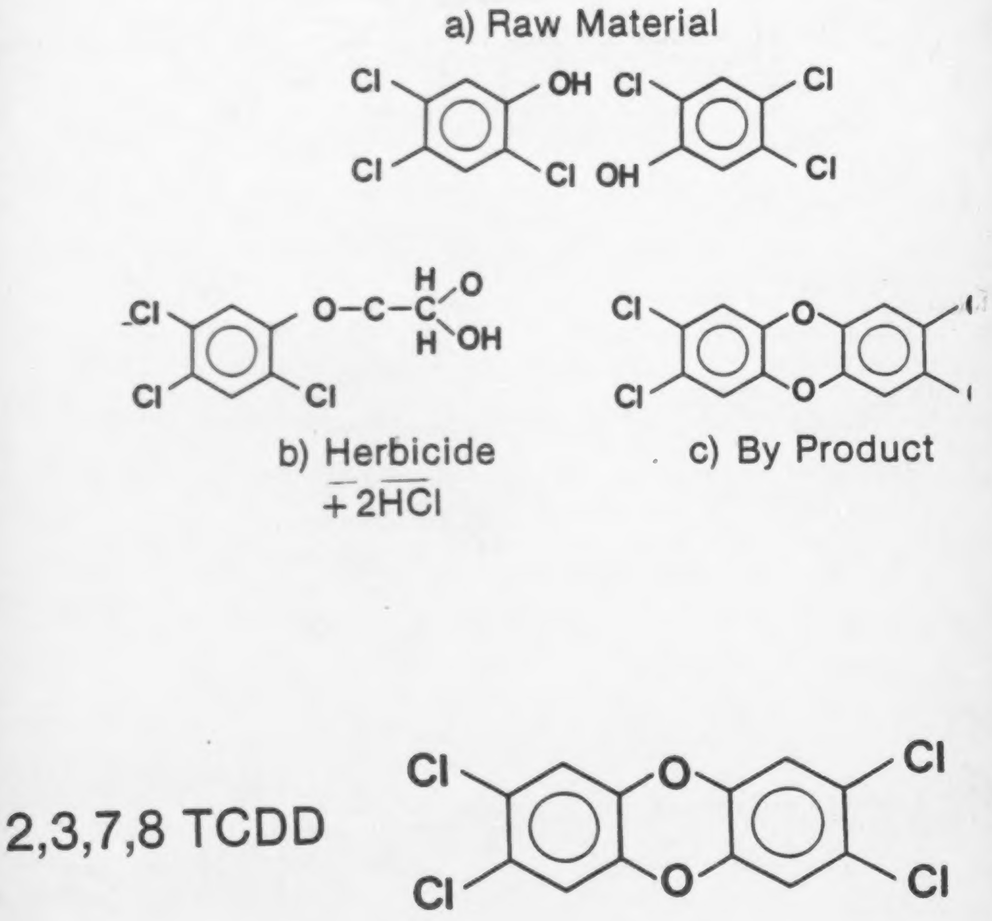

Cl
Cl
Cl
Cl
O
O

e) 2,3,7,8 TCDF



Cl=chlorine atom
The hexagonal structures with the circle is a benzene ring consisting of 6 carbon atoms.

Illustration of the formation of 2,3,7,8-TCDD (Dioxin) from the Raw Material (a) Trichlorophenol.


a) Raw Material
Cl
OH
Cl
Cl
Cl
Cl
Cl
OH
Cl
Cl
H
O
O–C–C
H
OH
Cl
Cl
b) Herbicide
+ 2HCl
Cl
O
O
Cl
c) By Product
2,3,7,8 TCDD
Cl
O
Cl
Cl
O
Cl

ARTICLE IN PRESS IN NEW JERSEY MEDICINE

DIOXIN EXPOSURE AND HEALTH: NEW ADVANCES AND OLD CONTROVERSIES

Michael Gochfeld, M.D., Ph.D., Michael Gallo, Ph.D., Peter Kahn Ph.D.

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ABSTRACT: The compound 2,3,7,8-tetrachloro-para-dibenzodioxin, also known as 2,3,7,8 TCDD, TCDD or simply "dioxin" is reputed to be the most toxic synthetic compound known based upon its lethal dose for guinea pigs. It is also a most potent inducer of microsomal enzymes which are resopnsible for metabolism of many endogenous and exogenous compounds. In laboratory animals TCDD affects many organ systems, and it has been studied extensively for its potential human health effects. The background level of TCDD in human adipose tissue averages 5 parts per trillion in developed nations. Most of our knowledge comes from relatively few studies of workers exposed during explosions, spills or fires. Inferences regarding low level, long term exposure are difficult and the significance of such exposures remains controversial.

In terms of extent of media coverage, "dioxin" can be viewed as the toxic chemical of the decade. The polarity of views on its toxicity include those who believe it is a clearly identified scourge(1), and those who believe that no significant human health problems are attributable to it(2-3). Federal agencies are in the throes of abandoning research into dioxin (Centers for Disease Control) or reevaluating their risk assessments (Environmental Protection Agency). Although the potential exposure of humans to dioxins was highlighted and focused by the widespread use of herbicides in Viet Nam, the problem of dioxin exposure is by no means unique to veterans of the Viet Nam war.

The controversy is heightened by the confusion in nomenclature. To a chemist a dioxin compound is one in which two moieties are linked by two oxygen bridges (see Figure 1A). Among the dioxins are those in which the moieties are two benzene rings, hence the term dibenzodioxins (Figure 1b). Almost all attention focuses on polychlorinated dibenzodioxins, particularly those with four or more chlorine atoms (Figure 1C shows a pentachloro dibenzodioxin). To the vast majority of people, however, the term dioxin is synonymous with the compound shown in Figure 1D, 2,3,7,8 tetrachloro-para-dibenzodioxin. One also sees this compound abbreviated as TCDD (although there are two other tetrachloro isomers), or more correctly as 2,3,7,8-TCDD. In this paper we will use the term 2,3,7,8-TCDD and dioxin synonymously, while "dioxins" will refer to polychlorinated dibenzodioxins in general. A closely related class of compounds are the polychlorinated dibenzofurans, distinguished from dioxins by the single oxygen bridge (Figure 1E).

It is possible to distinguish Industrial versus Environmental Exposure, and Acute versus Chronic Exposure. Acute Industrial exposures occurred with accidents in Newark, New Jersey, at Nitro, West Virginia, and Seveso(4), Italy, the latter causing extensive environmental contamination as well. Acute Environmental exposures occurred during spraying of 2,3,7,8-TCDD-contaminated defoliants.

Although such exposures are dramatic, the public has been more concerned with long-term low level exposure, not so much in the workplace (although many workers were exposed to dioxins for long periods of time), but in the community and, of course, in Viet Nam(5). Although the saga of the Viet Nam veteran has been a long-time unfolding, community exposure has been emphasized by such well-publicized events as Times Beach, Missouri(6) and the Iron Bound section of Newark, New Jersey. Perhaps the most familiar of the "dioxin incidents" was the contamination of Times Beach, Missouri by 2,3,7,8-TCDD which resulted in a Federal government decision to buy out all the residents of that town(6). The occupational and community contamination of the Iron Bound section of Newark has been extensively studied. A major difference between Times Beach and Newark 2,3,7,8-TCDD episodes is that in the sandy soil of the former the 2,3,7,8-TCDD was readily bioavailable, while the more complex "organic" soil of Newark held the substance more tenaciously rendering it mostly biologically unavailable, and therefore reducing its risk (7-8).

SOURCES OF DIOXIN EXPOSURE

Chlorinated dibenzodioxins arise in a variety of settings, particularly as a result of combustion under natural as well as artificial conditions(9) or through reaction of chlorinated aromatic compounds. Public attention has recently focused on garbage incineration as a source of dioxin fallout. More dramatic has been the issue of dioxin exposure of veterans exposed to herbicides. Whereas there are many dioxins formed during incineration, the dioxin contaminant of herbicides is almost exclusively 2,3,7,8-TCDD.

Agent Orange was a mixture of two common garden herbicides, 2,4-D and 2,4,5-T (trichlorophenoxyacetic acid). During synthesis of the latter (Fig 2b) from 2,4,5-trichlorophenol (Fig 2a) a certain amount of 2,3,7,8-TCDD was produced as shown (Fig 2c). The configuration of the chlorines on the trichlorophenol assured that it is only the 2,3,7,8 isomer that was accidently produced. The same dioxin has been found as a contaminant of hexachlorophene. During the production of pentachlorophenol the octachloro dibenzodioxin was produced as a byproduct.

TOXICITY

The 2,3,7,8-TCDD has the reputation as the most toxic synthetic compound known . The position of the chlorine atoms on the two benzene rings influences the conformation of the molecule and its toxicity. Moreover, different species of experimental animals vary widely in their vulnerability. The toxicity of other dioxin compounds is often expressed relative to 2,3,7,8-TCDD as TCDD equivalents, although this convention is being abandoned as too simplistic. Among the experimental species the guinea pig has proven the most sensitive. The lethal doses for mice and rats tend to be 1000-10,000 times higher than the lethal dose for guinea pigs.

HEALTH EFFECTS

The controversy over the magnitude of the 2,3,7,8 TCDD impact on human health focuses on whether human susceptibility is more similar to the guinea pig or to the mouse. The spectrum of health effects attributed to 2,3,7,8 TCDD can be categorized as: death, chloracne, cancers, hepatotoxicity, immunosuppression, porphyria, neurobehavioral and psychological changes and miscellaneous.

Chloracne, a potentially severe skin disease is the most characteristic human disorder caused by dioxins. The basic biology of the skin is altered, and the disease may last for decades, even after the cause is removed. Clinically chloracne is difficult to distinguish from other acneiform lesions, and diagnosis is based on its distribution, duration, and history of exposure. It most often results from acute exposures to chlorinated aromatic compounds (10). Some authorities argue that if chloracne doesn't occur, one needn't worry about dioxin exposure. This view is not widely accepted, for in animals other conditions may arise from chronic lowlevel exposure, even though chloracne doesn't develop.

2,3,7,8-TCDD is an animal carcinogen (11-12). Several different kinds of cancer have been produced, and it appears to have both initiation and promotion effects (i.e., it can itself initiate the development of a new tumor in the absence of any other chemical, and it can also facilitate the development of a tumor initiated by another chemical carcinogen). In humans, however, the evidence for cancer causation is controversial. Cancers of the connective and related tissues, called soft-tissue sarcomas, have been attributed to dioxins(13-14), but some studies have questioned this relationship (15). More recently Hodgkins disease and non-Hodgkin's lymphomas, have been attributed to chlorinated phenoxyacetic acids, with the suspicion that dioxins may contribute. An unpublished Veteran's Administration study has showed that marines who served in Viet Nam have experienced an excess mortality due to lung cancer and non-Hodgkins lymphomas(16). Thus although the carcinogenic potential of 2,3,7,8-TCDD is recognized its relation to human cancers is unclear. Complacency is not warranted.

There is evidence that dioxin exposure interferes with the body's normal cell-mediated immune mechanisms, and could render it more susceptible to disease. Moreover, the metabolism of porphyrins, chemicals derived from the normal breakdown of hemoglobin, is altered, and certain people with dioxin exposure may suffer from the porphyria(17). In experimental animals liver disease can be produced by dioxin treatment, and cases o. liver damage have been reported in exposed humans as well. 2,3,7,8-TCDD is among the most potent inducers of microsomal enzymes yet identified, and thus is capable of altering the metabolism of endogenous agents such as hormones as well as exogenous agents such as foods and environmental chemicals. .

Another significant effect in animal experiments is the teratogenic effect, for dioxins can interfere with gestation resulting in miscarriages, stillbirths, or abnormal offspring(19-20). Animal experiments show abnormalities occurring at very low exposure levels. The interpretation of epidemiologic studies of birth defects and adverse reproductive outcomes among Viet Nam veterans is controversial(21-22), and in any case the exposure data in such studies was inadequate. Although as yet there are no data incontrovertibly showing reproductive effects in humans with 2,3,7,8-TCDD exposure, that is certainly one of the major concerns voiced by the Viet Nam veterans.

The main studies now being conducted on human populations include a National Institute of Occupational Safety and Health study of herbicide manufacturing workers, and studies of Viet Nam veterans who are believed to have seen significant exposure to Agent Orange, and thereby to dioxin. Studies of the latter are being conducted by the U.S. Air Force, by the Veterans Administration, and by various states, including the New Jersey

Agent Orange Commission(23). These studies will focus on a variety of health effects: biochemical, physical and psychological .

THE POINTMAN PROJECTS

The New Jersey "Pointman I" study has demonstrated that even 15-20 years after presumed exposure veterans who handled herbicides in Viet Nam had significantly higher levels of 2,3,7,8-TCDD in their adipose tissue and blood (averaging greater than 40 parts per trillion and in some cases above 150 parts per trillion) compared with non-exposed veterans and the general population whose levels average about 5 parts per trillion(31). Most importantly there were no significant differences for other dioxin and dibenzofuran compound(24), supporting the supposition that the source of the elevated TCDD was their Agent Orange exposure.

The first Pointman study was predicated on the fact that the gold standard for body burden of 2,3,7,8-TCDD is its concentration in adipose tissue. Lipophilic or hydrophobic compounds naturally concentrate in fatty tissues or cells. The research showed clearly, however, that the concentrations of TCDD in the blood lipids are not appreciably different from the concentration in fat, and the correlation between the two is very high, > 0.8 in the Pointman study and > 0.9 in a comparable C.D.C. study(25). The Pointman study used a 24 hour fast prior to drawing the blood, but a second study of the same group of men showed no difference in blood levels with and without fasting(26). Accordingly, future studies of dioxin in humans can be based on spot blood samples. However, in order to have adequate sensitivity in the parts per trillion range, the analysis requires over 300 ml of blood, at the present time.

'An important factor in understanding the dynamics and health effects of dioxins is their half life in the human body. Assuming that an individual had a single exosure, what is the decay curve that characterizes the substance. Recent evidence obtained by the C.D.C. suggests that the half life may be 7 years(25). However, there are good metabolic reasons for believing that a first order decay curve is not appropriate for the elimination of these compounds from the body, in which case the true half life may be much longer. Given a 7 year half life, the observation of a level in excess of 150 parts per trillion in a Viet Nam veteran in 1985 can be extrapolated back to a level of 600 parts per trillion in 1971.

Occupationally exposed groups are also being investigated by the National Institute for Occupational Safety and Health. This study is focusing on about 500 workers in the herbicide-manufacturing industry in New Jersey and Missouri as well as appropriate controls. The results of this study are anticipated in 1988.

INCINERATION

About 15 years ago researchers for the Dow Chemical Corporation showed that various dioxins are produced by the incineration of both natural and synthetic products (9). The potential for airborne dioxin contamination from incineration arises from the fact that combustion of common organic materials, including wood, paper, and plastic products (some of which contain chlorinated dioxins to begin with) results in the chemical formation of various pyrolysis compounds including dioxins. These dioxins are not destroyed unless high temperature levels are maintained for adequate time periods. The two physical factors: high temperature and "residence" time in the burner, determine whether the dioxins (and other polyaromatic hydrocarbons such as PCB's) will themselves be destroyed.

A variety of incinerators has been studied with respect to chemical contaminants in the ash and airborne emissions, and dioxins are among the pollutants found(27). Although present, 2,3,7,8-TCDD is not the major dioxin constituent. Risk assessments have been developed for dioxin contamination from incineration, but the exposure data are still very sparse. Some of the other types or isomers are nearly as toxic and occur in greater quantities. Thus far, in most cases, the amount of total dioxins has been below the parts per billion range([illegible]3). Technological developments added on to incinerators could be used to reduce the dioxin contamination even further. Some new facilities claim to utilize such devices.

TCDD has a tendency to adhere to fine particulates emerging from a stack. Using a variety of assumptions, statistical modelling approaches, and very limited risk analysts have concluded that such resource recovery facilities do not pose a hazard to residents living in the immediate vicinity (27). Results obtained from monitoring the Hempstead, New York recovery plant revealed concentrations of 2,3,7,8 TCDD ranging from non-detectable (ND) up to 3.5 ng/cu.m.

In our view the medical community has not yet been provided with sufficient scientific data to form an opinion on the safety of garbage incinerators with respect to dioxins or other substances. The requisite information would include extensive environmental monitoring of the air emissions from a variety of facilities over a long period of time. Usually the data available include just a few of the contaminants, monitored perhaps once or twice per year. If, for example, a company only measures the 2,3,7,8 TCDD, there will be no information on the other highly toxic dioxins which may be present in even greater amounts. Similarly, if a measurement is only made once or twice, just after the facility has started up (when it may be at peak efficiency), there is no way to predict what kind of emissions to expect in the weeks just prior to its annual maintenance. Nor is there any indication of the importance of human factors, always a fragile link in a technological system, in maintaining operating conditions at specifications.

We believe that in principal it should be possible to construct safe incineration systems, but there is a void between the theory and the realization. A variety of assurances are required before the medical community can rest in comfort that a particular incineration facility poses no health hazard to the surrounding community. New Jersey's Hazardous Substance Management Research Center based at the New Jersey Institute of Technology is in the forefront of research on technology for safely destroying such hazardous chemicals and for assuring that environmental contamination problems do not occur. Moreover, recent research suggests that the concern with dioxin may cause people to overlook other hazards related to incineration emissions such as heavy metals, particularly chromium, which are not destroyed by incineration(38).

DIOXIN IN NEWARK

In 1982 studies of TCDD levels in fish and crabs from the Passaic River and Newark Bay lead the New Jersey Department of Environmental Protection to a hitherto unsuspected dioxin-contaminated site(29). The former Diamond Shamrock facility on Lister Avenue in the Ironbound Section of Newark had been a manufacturing site for phenoxyherbicides, and in the wake of industrial accidents and onsite disposal, much of the ground on the property and along access roads was contaminated with 2,3,7,8 TCDD. More than one million dollars was spent on soil analyses and site "mitigation" procedures, and State and Academic experts spent much time evaluating the potential for human exposure in terms of the then available data and risk assessments.

The dioxin in Newark was present in the soil, and human exposure would require either that dioxin-bearing dust became airborne and was inhaled, or that people ingested the soil or were exposed through the skin. Since dioxin is not readily absorbed through intact skin, attention has focused on inhalation and ingestion. Accordingly one of us (Gallo) proposed a study of the bioavailability of the dioxin in the Newark soil, and found that the toxicity of the contaminated soil fed to guinea pigs was 50 times lower than would have been expected from the dioxin concentration(7). He concluded that the dioxin in this soil had low bioavailability due to its binding to oily material also present in this soil, and then demonstrated that dioxin in soil from Times Beach, Missouri (another dioxin-contamination site), was much more bioavailable(8).

In view of the uncertainty that human exposure had actually occurred a health study of this community has been deferred, and attention has focused instead on the former employees of the company who almost certainly would have had a high level of exposure. These workers are now being examined by N.I.O.S.H.

THE PROBLEM: EVALUATING CAUSATION

We identify four problems that have impeded development of a clear statement of human health risks associated with 2,3,7,8 TCDD:

1. The first lies in the extreme difficulties involved in adequate laboratory assay of dioxins(30). In view of the great toxicity of these materials, few laboratories are equipped to handle the standards

necessary. Moreover, the dioxins are present at the parts per trillion level, which would tax the sensitivity and precision of any laboratory. In such a market place the cost for a single dioxin analysis is measured in the thousand dollar range, and one is thus limited to making only a few measurements in any one incident, or worse one may have no measurements at all, which makes it very difficult to evaluate exposure levels and dose-response relationships. Thus we are denied access to one of the basic strategies of the environmental toxicologist, the measurement of exposure. New Jersey is now making strides to improve the availability of highly sensitive analytical capabilities at reasonable cost.

2. We are confronted by a health effects literature with widely divergent reports may be accompanied by unspoken biases. In part, this reflects that fact that the authors did not know the true exposures, hence in "negative studies" some of the people with no symptoms or signs may not have been truly exposed, while the same could be said for "positive studies".

3. The long latency of some problems attributed to dioxins, particularly cancers, means that adequate time has not yet elapsed to allow a true measure of the ill effect. Hence scientific reports of certain cancers produced by dioxins in animals and perhaps in Vietnamese people(31) are therefore disquieting.

4. Finally we still do not have a clear picture of how to extrapolate the effects of dioxin on laboratory animals to predict the effects in humans. The U.S. Environmental Protection Agency has recently revised its estimate of the human risk from dioxin exposure, concluding that TCDD is only about 1/16th as dangerous as previously estimated.

The first two of these problems are more or less unique to TCDD while the last two typify our problems with many environmental toxins.

CLINICAL EVALUATION OF "DIOXIN EXPOSURE"

There is an increasing clamor among veterans and community residents to determine whether they have had significant exposure or adverse health effects due to a host of environmental pollutants, including 2,3,7,8-TCDD. From the above discussion it is apparent that such an evaluation is fraught with difficulty.(32) Diagnosis of chloracne certainly suggests exposure to chlorinated aromatic compounds, but 2,3,7,8-TCDD is only one of several compounds that could be implicated, and is seldom present in sufficient concentration or quantity to induce chloracne. No other "sentinel" or diagnostic criteria have been established.

One approach would be to focus on evaluating those systems on which chlorinated aromatic compounds have a known impact, namely liver function, prophryin excretion patterns, and cell-mediated immunity. In our experience, however, the main concerns of individuals who have had or suspect chemical exposure of any kind, including TCDD, are cancer and birth defects.

The ability of the clinician to assess such risks and, if appropriate, to reassure an anxious individual is limited. Introduction of test systems such as DNA-adducts which determine whether an individual's DNA has covalently bound dioxin might reveal individuals with an enhanced risk. Such techniques are indeed on the horizon, but probably will not be practical on a large scale within the next decade.

More realistically the clinician must make sufficient enquiries to determine the dose or exposure which a patient has encountered. Thus even being in the presence of a highly toxic material such as 2,3,7,8-TCDD will have little impact if there has been no actual exposure. The recent studies showing low bioavailability of 2,3,7,8-TCDD in certain soils is an important indication that dioxins may be present without posing a significant health hazard(58).

In the absence of a definitive evidence of exposure a clinician must explain to a patient the uncertainty regarding risk. One may feel comfortable in reassuring rather than alarming a patient, but ultimately the fact remains that we have neither clear evidence of health effect nor grounds for complacency. Detailed health and exposure studies must be carried on to provide answer(s). They may also identify for the patient the sources of exposure that are to be avoided, particularly the consumption of contaminated foods or direct contact with contaminated soil.

CONCLUSION

The dioxin issue remains a significant public health problem. While epidemiologists continue to explore the impact of dioxin exposure on human populations, health educators need to be at work putting dioxin contamination into perspective. It appears safe to say that despite its intrinsic toxicity, a major human health impact of dioxin has not yet been demonstrated. This has prompted the C.D.C. to abandon studies of Viet Nam veterans, prematurely we think.

Whether or not a causal link to human disease is shown, dioxin has clearly served to raise the environmental consciousness of a generation, but it should not detract critical attention from other environmental contaminants which pose more significant health hazards.

Whatever the final verdict(s) regarding human disease attributable to

2,3,7,8-TCDD it has had and continues to offer important lessons for environmental and occupational medicine and toxicology. Probably no other single substance, not even lead, asbestos, or benzene all of which more clearly cause significant disease, has attracted more scientific and non-scientific attention in such a short period of time.

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FIGURE LEGENDS

Figure 1. (a) general chemical structure of a dioxin compounds, with two organic moieties bridged by two oxygen atoms; (b) a generalized dibenzodioxin with the standardized numbering of the carbon positions; (c) the compound 1,2,3,7,8 pentachloro dibenzo dioxin; (d) 2,3,7,8 tetrachloro-para-dibenzodioxin, the compound comply referred to as TCDD or "dioxin"; (d) the 2,3,7,8 tetrachlrodibenzo furan, revealing the single oxygen bridge of the furan compounds.

Figure 2. Pathway for the synthesis of the herbicide 2,4,5 trichlrophenoxyacetic acid (b) from two molecules of the raw material (2,4,5 trichlorophenol [a], resulting also in the formation of the unwanted by-product, 2,3,7,8-tetrachloro dibenzo dioxin (c).

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Original Contributions

Dioxins and Dibenzofurans in Blood and Adipose Tissue of Agent Orange–Exposed Vietnam Veterans and Matched Controls

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Vietnam veterans who were heavily exposed to Agent Orange exceeded matched control subjects in both blood and adipose tissue levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) but not in the levels of the 12 other 2,3,7,8-substituted dioxins and dibenzofurans that were detected. Since only TCDD among these compounds was present in Agent Orange but all are present in the population of the industrialized world, it is likely that the elevated TCDD levels arose from wartime exposure. The high correlation ($r = +.89$) of blood with adipose tissue level suggests that there may be a mobile equilibrium between them and that blood measurement could replace adipose tissue measurement of TCDD levels, making the collection of human data less invasive.

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ESTABLISHING the existence or absence of health effects in populations that are exposed to low levels of toxic chemicals is made difficult by a number of factors. Among these classification of study subjects into exposed and unexposed groups often is a major problem, which is compounded by the fact that exposure may have occurred long before the study commences. Since classification errors dilute the effects one seeks to measure, negative epidemiologic results leave open the question of whether the correlation between exposure and toxic end point is absent or whether classification errors made it undetectable. Studies of Vietnam veterans,[1,2] some of whom were exposed to the defoliant mixture known as "Agent Orange," which was contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) during the manufacture of its 2,4,5-trichlorophenoxyacetic acid herbicide component, may very well suffer from this problem.

With the discovery by Rappe et al[3,4] that survivors of the Yusho accident[5] in Japan had detectable traces of dibenzofurans in their blood 11 years after consuming contaminated cooking oil, it became apparent that chlorinated multiring aromatic compounds can have long half-lives in human tissues. (In Japan in 1968, rice oil, which is used in cooking, became contaminated during processing by a polychlorinated biphenyl–based heat exchange fluid. The fluid, in turn, contained small amounts of chlorinated dibenzofurans, leading to a total dibenzofuran content in the rice oil of 5 ppm.) The results suggested that measurement of tissue levels in persons who were exposed in the distant past might confirm exposure status.

In early 1984, Rappe et al[6] reported 14 polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) in samples of human adipose tissue from northern Sweden. The compounds had between four and eight chlorines, and all were substituted at the 2, 3, 7, and 8 positions. Laboratories on three continents have since confirmed these observations, and it is now accepted that there is a background of these compounds in the population of the industrialized world.[6-11] Among these substances, however, only 2,3,7,8-TCDD was present in Agent Orange so that isomer-specific measurement of the entire series should provide us with both positive and negative controls in correlating tissue levels with exposure status, as only 2,3,7,8-TCDD levels would be expected to be elevated in herbicide-exposed men.

Halogenated dibenzodioxins and dibenzofurans are lipid soluble and tend to accumulate in adipose tissue. Most

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studies have therefore analyzed fat, which requires obtaining the sample by surgical biopsy. A less invasive assay would allow rigorous epidemiologic examination of the relationship between low-level exposure and subsequent health effects in a large number of people, as suggested by Schecter et al.[11]

A program to compare exposure of Vietnam veterans to Agent Orange with their 2,3,7,8-TCDD body burdens and with their health statuses has therefore been undertaken by the State of New Jersey and is known as the "Pointman Project." The present pilot study was designed primarily to determine, by isomer-specific analysis of all tetrachlorinated to octachlorinated dibenzodioxins and dibenzofurans, whether there is a relationship between exposure and 2,3,7,8-TCDD levels in Vietnam veterans who were exposed to Agent Orange 15 to 20 years ago and whether blood and adipose tissue levels are correlated.

PROCEDURES

Study Groups

Twenty-seven men were studied. Ten were heavily exposed Vietnam veterans, nine of whom handled herbicides regularly while in Vietnam. We emphasized spray handlers at this stage of the investigation rather than ground troops who served in sprayed areas to maximize the likelihood of finding 2,3,7,8-TCDD. Ten Vietnam veterans who had little or no exposure served as Vietnam control subjects. Seven veterans who served during the time of the Vietnam War but who did not go to Southeast Asia served as Vietnam-era control subjects. Era control subjects were included to ensure that if something in Vietnam other than herbicide exposure led to elevated 2,3,7,8-TCDD levels we would be able to detect it.

Each control subject was matched against an exposed veteran for the following four factors in addition to sex: age at time of entry into the study ± 36 months, dates of military service ± 36 months, race/ethnicity (black, white, or Hispanic), and rank (all participants were enlisted men). There was thus one Vietnam control subject for each exposed subject and one era control subject for each of seven of the exposed men. We were unable to find suitable matched era control subjects for three of the exposed men.

Subject selection was initiated with a broad request for potential participants through the mass media, veterans' service organizations, and church and community groups. There were approximately 2700 respondents who completed a short questionnaire that provided age, dates of service, dates in Vietnam, race, branch of service, military unit, and limited information about exposure. From this group we identified 100 men who seemed likely to have handled herbicides during a tour of duty in Vietnam. These men were sent a 30-page questionnaire detailing all military assignments in and out of Vietnam, all civilian occupations, hobbies, diet, and other activities that might influence exposure. Eighty-four questionnaires were returned. The returned questionnaires were reviewed by a selection committee that included the principal investigators (a biochemist and an occupational physician), a psychologist, and two veterans with broad knowledge of conditions in Vietnam. The committee excluded those with confounding exposures and selected those who seemed to have the highest likelihood of exposure in Vietnam, but not elsewhere. We then sent the same questionnaires to potential Vietnam and era control subjects from among the original 2700 respondents who were appropriate matches for the exposed men.

We used the ten men with the highest exposure for whom we could obtain Vietnam control subjects, and for these we found suitable era control subjects for seven. Informed consent was obtained from all subjects after the nature of the study and its possible consequences had been explained in detail.

Military exposure status was confirmed for Vietnam veterans (both exposed men and Vietnam control subjects) by the US Army/Department of Defense Joint Environmental Support Group. The Environmental Support Group confirmed exposure status by ascertaining whether the veteran had a job title that entailed potential exposure as a handler of herbicides. In the one case of an infantryman who was not a spray handler, his presence in areas sprayed by known herbicide missions was verified by the Environmental Support Group. Partly because of the emphasis on spray handlers and partly because of the methods of subject selection, this pilot study is not representative of all Vietnam veterans. Because exposure status was verified, however, we believe that recall bias does not affect the correlation between exposure status and body burden as found by chemical analysis, as both are objectively determined.

Five of the men were members of Operation Ranch Hand, the Air Force unit that flew fixed-wing aircraft on spray missions. Three of these were ground personnel who maintained the aircraft and spray equipment and who filled the tanks with herbicide. The other two operated the spray equipment in flight. A sixth man was an Air Force freight handler who handled drums of defoliants. Two men were Army chemical corps specialists. One man was an Army helicopter crew chief who filled defoliant tanks and flew spray missions. The tenth man was an army light infantry combat soldier with a reported history of herbicide exposure.

Groups of three to six subjects were admitted to the hospital for 3½ days of medical testing, during which they were examined by specialists in occupational and internal medicine, dermatology, neurology, psychology, and psychiatry. A battery of clinical tests also was done, including a study of immune function, and samples of adipose tissue and blood were taken for analysis, as described later herein. The results of the medical testing will be published separately.

Tissue Sampling

Ten to 20 g of subcutaneous tissue were biopsied by liposuction and transferred immediately to hexane-washed polypropylene containers, which were stored frozen. To increase the likelihood of finding 2,3,7,8-TCDD and its congeners in the blood, each subject fasted for 24 hours in an attempt to mobilize TCDD from stored fatty reserves. Following the fast, 300 to 400 mL of blood were drawn into heparin as anticoagulant (see later herein). Serum fatty acids were monitored at 12-hour intervals during the fast as an index of fat mobilization.

Care was taken to minimize the time that blood was in contact with the plastic blood-drawing apparatus to minimize leaching of plasticizer. The standard hospital blood bags that were used had been preloaded with anticoagulant solution, which we removed, using the first 10 to 15 mL of blood as rinse. The rinse was discarded. Fresh heparin was added, and collection continued. The blood was transferred promptly from the bags to hexane-washed glass containers that were stored on ice during transport to the laboratory in New Brunswick, NJ. Red blood cells were separated by centrifugation at 4°C, yielding plasma samples of 150 to 160 mL for chemical analysis. The plasma was placed in hexane-washed polypropylene containers and stored frozen until analyzed.

Sample Coding and Handling

An independent referee team of two people who were not associated with any of the institutions or individuals participating in the study coded and relabeled the samples and returned them to the investigators for shipment

Table 1.—Blood Validation Test Analyses (Levels in Picogram of Analyte per Gram of Blood Fat)

Isomer*	Mean	SEM
2,3,7,8-TCDF†	3.67	0.36
2,3,7,8-TCDD†	4.59	0.25
2,3,4,7,8-PeCDF	28.42	0.88
1,2,3,7,8-PeCDD†	12.42	0.43
1,2,3,4,7,8-HxCDF†	5.50	0.29
1,2,3,6,7,8-HxCDF	4.75	0.28
1,2,3,7,8,9-HxCDF	2.85	0.31
1,2,3,4,7,8-HxCDD	15.59	0.77
1,2,3,6,7,8-HxCDD†	56.50	1.54
1,2,3,4,6,7,8-HpCDF†	13.81	0.67
1,2,3,4,6,7,8-HpCDD	58.73	2.30
OCDD†	395.88	10.67

*TCDF indicates tetrachlorodibenzofuran; TCDD, tetrachlorodibenzo-p-dioxin; PeCDF, pentachlorodibenzofuran; PeCDD, pentachlorodibenzo-p-dioxin; HxCDF, hexachlorodibenzofuran; HxCDD, hexachlorodibenzo-p-dioxin; HpCDF, heptachlorodibenzofuran; HpCDD, heptachlorodibenzo-p-dioxin; and OCDD, octachlorodibenzo-p-dioxin.

†All samples were spiked with the seven carbon 13–labeled standards that are marked. The table, however, shows levels of the unlabeled compounds originally present in the sample and detected in the validation analysis.

Table 2.—Means and SEMs for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin Levels

	Groups			
	Exposed Subjects	Vietnam Control Subjects	Era Control Subjects	Pooled Control Subjects
	Adipose Tissue Levels, pg/g Tissue Wet Weight			
No. of subjects	10	10	7	17
Mean	41.7	5.1	3.2	4.3
SEM	16.8	1.4	0.5	0.9
Median	15.4	5.4	3.5	4.5
	Blood Plasma Levels, pg/g Blood Fat			
No. of subjects	9	10	7	17
Mean	46.3	6.6	4.2	5.7
SEM	19.1	0.9	0.8	0.7
Median	25.1	5.3	3.9	4.6

to the University of Umeå in Sweden, where the chemical analyses were performed. There was no relationship between blood and adipose tissue sample numbers. The analytic laboratory and the principal investigators were thus blind to the exposure statuses of the men from whom the samples came. All analytic results were deposited with the referee team before the code was revealed. A consequence of the coding was that no analyses could be repeated, and there was not enough material for replicates.

Chemical Analysis

Adipose Tissue.—Sample extraction and containment enrichment were by the method of Stalling et al[12] and Smith et al,[13] with minor modifications.[14]

The analytic method has been shown in an interlaboratory study[15] to have a high degree of quantitative and qualitative reliability. It also has been validated by analyzing fish, cow's milk, and human milk fortified at different levels with known amounts of carbon 13–labeled standards[16] (C. Rappe, P.-A. Bergqvist, R. Andersson, et al, unpublished data, 1986).

High-resolution gas chromatography/mass spectrometry conditions were as described.[5,15] In the present study, selectivity was enhanced over the interlaboratory study[15] by using a double-focusing mass spectrometry instrument (model 70-250, VG Limited, Manchester, England) operating at a resolution of 6000 to 8000 daltons. The background reduction produced by this instrument also results in higher sensitivity. Isomer separation was achieved by using 60-m columns (model SP2330 or SP2331, Supelco Inc, Bellefonte, Pa).[17] Every third sample was a system blank. All samples were run in electron impact mode with selective ion monitoring.[18]

Blood.—The extraction of blood plasma was based on partitioning in a system of chloroform, methanol, and water. The procedure is a modification of the method of Bligh and Dyer.[19] Solvent was evaporated from a known amount of extract and the lipid that remained was weighed to determine the fat content of the plasma. The fat was removed on a silica column that was eluted with hexane and the extract was cleaned on a carbon column (Carbopack C, Supelco Inc, Bellefonte, Pa) that adsorbs the PCDDs and PCDFs. They were eluted from the carbon column in toluene. High-resolution gas chromatography/mass spectrometry conditions were the same as for adipose tissue.

Validation of Blood Plasma Analysis.—A pooled plasma sample from the Regional Hospital in Umeå was used for a validation study. The sample was divided into 12 aliquots that were analyzed individually. Each was fortified with a standard mixture containing equal amounts of seven $^{13}C_{12}$-labeled PCDDs and PCDFs, which are marked with a dagger in Table 1. On a plasma basis, four spiking levels were used: 0.018 parts per trillion (ppt), 0.058 ppt, 0.18 ppt, and 0.58 ppt of each analyte in the mixture. Three aliquots were spiked at each level, yielding triplicate analyses. For each sample the recovery of the standards was used to compute the levels of the "natural" carbon 12–labeled PCDDs and PCDFs, resulting in 12 readings for each compound. The gas chromatography/mass spectrometry analyses were performed in the same way as for adipose tissue. The analyses agree with one another quite well (Table 1).

Surrogates for Unknowns.—For the veterans' samples two ^{13}C-labeled standards were used: $^{13}C_{12}$-labeled 2,3,7,8-TCDD and octachlorodibenzo-p-dioxin. The protocol was fixed as of December 1984, at the time that the first men entered the hospital. At that time other ^{13}C-labeled surrogates were not readily available. Although they have since become available, we thought it better not to change the protocol once analyses had commenced.

The results have been corrected for recovery of the labeled surrogates. For $^{13}C_{12}$-labeled 2,3,7,8-TCDD the recovery from plasma was normally 60% to 70%. The recovery of $^{13}C_{12}$-labeled octachlorodibenzo-p-dioxin from plasma was much lower, being about 20% in some blood samples. Recoveries of both standards from adipose tissue ranged from 68% to 74%. Blood levels are expressed per gram of blood lipid. Adipose tissue levels are presented per gram of wet tissue. The detection limit for both blood and adipose tissue was 1 pg or less per gram of fat. In blood, which is approximately 1% fat, this corresponds to a detection limit of 0.01 pg/mL of whole blood. The analytic methods for blood are described in greater detail by Nygren et al.[20]

RESULTS

The levels of 2,3,7,8-TCDD in the exposed men exceeded those in the pooled control subjects by a wide margin in both blood ($P<.01$) and adipose tissue ($P<.001$) (Table 2). The Mann-Whitney *U* test was used to compare the exposed with the pooled control subjects. Although TCDD levels in the Vietnam control subjects exceeded those in the Vietnam-era control subjects, the difference was small and not significant.

In adipose tissue, the 2,3,7,8-TCDD levels in the exposed men exceed the levels in their matched Vietnam control subjects in nine of the ten pairs (Fig 1, left). The binomial probability of finding nine of ten subjects with an a priori probability of .5 is less than .01.

Because of technical problems with the blood sample from the exposed individual in trio 5 in Fig 1, right, only nine pairs comprising an exposed man

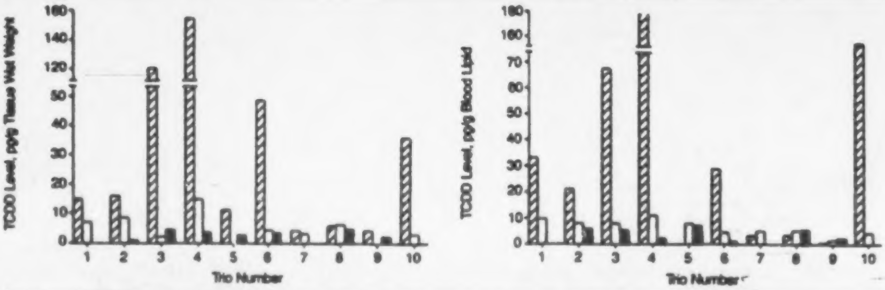

Fig 1.—Comparison of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) levels in adipose tissue (left) and blood plasma (right). Each bar represents a sample from one man. Note absence of Vietnam-era control subjects (closed bars) in trios 1, 7, and 10. Broken bars indicate broken Y axis; continuous bars, continuous part of axis; slashed bars, exposed individuals; and open bars, Vietnam control subjects. No levels in blood plasma are presented for exposed individual No. 5.

and a Vietnam control subject were suitable for comparison. In six of these the exposed men exceeded their Vietnam control subjects in 2,3,7,8-TCDD level (.10>*P*>.05).

Figure 2 presents the mean ± 1 SEM for each of the analytes in fat and blood by exposure status. In both fat and blood there is a strikingly higher level of 2,3,7,8-TCDD in the exposed men (Table 2). None of the other compounds exhibited this pattern in fat. In blood, other compounds seem to be somewhat higher in the exposed men than in one or both groups of control subjects. While the origin of this effect was not identified with certainty, some of it, at least, was due to recovery problems in the ^{13}C-labeled surrogates. This is especially likely for octachlorodibenzo-*p*-dioxin, for which the blood recoveries were low, as mentioned previously herein. In any case none of these differences are as striking as that found for 2,3,7,8-TCDD.

Figures 3 and 4 compare blood and fat levels of 2,3,7,8-TCDD. As mentioned previously herein, only seven trios could be completed due to lack of a sufficient number of era veterans who were acceptable as matches, who had no evidence of civilian or military exposure, and who were available. There were thus 17 control subjects and, because of the failure of the analysis on the blood of one exposed individual, nine exposed veterans who were suitable for the comparison. In Fig 3 all 17 control subjects fall in the domain bounded by blood and fat levels of 15 pg/g. Only three of the nine exposed men were in this range. The result is significant (Fisher's exact test, *P* = .001).

The data for the group as a whole, exposed and control subjects taken together, are not normally distributed, so a logarithmic transformation was used. The correlation coefficient for the transformed data was .72 for all 26 points. Because untransformed values close to zero are sensitive to variation in laboratory analysis and have a large effect on the log value, Fig 4 shows the logarithmic regression for men with both blood and fat levels greater than or equal to 1 pg/g. The correlation coefficient for these 22 points was .89. The least squares regression yields the following:

$$\log \text{(adipose tissue level)} = 0.86 \times \log \text{(blood fat level)} + 0.10$$

The SEs for the slope and intercept are 0.10 and 0.25, respectively. The slope is significantly different from zero at the *P* = .0001 level but not different from 1.0, and the intercept does not differ significantly from zero. Some of the scatter in the figure is probably due to the presence of nonlipid components in the adipose tissue samples. The 2,3,7,8-TCDD levels in fat and blood are similar if the blood levels are expressed on a per gram of blood fat basis.

COMMENT

One of the most striking results is that Vietnam veterans who were heavily exposed to Agent Orange exceed matched control subjects in 2,3,7,8-TCDD levels 15 to 20 years after exposure (Table 2 and Fig 1). A comparison of their 2,3,7,8-TCDD levels with the levels found for other isomers (Fig 2), moreover, makes it highly likely that the elevated TCDD levels in the exposed men are due to their wartime exposure to the defoliant. It is thus clear that the compound has an extremely long half-life in human beings, considerably longer than the one-month half-life found in laboratory rodents.[illegible]

Gross et al[illegible] measured adipose tissue levels of three Vietnam veterans designated as heavily exposed and of several control veterans. Theirs was a feasibility study whose object was to determine the range of levels that might exist in the men, so the control subjects were not matched individually to exposed subjects. Although the nature of the heavy exposure was not stated, they found a range of 20 to 173 pg of 2,3,7,8-TCDD per gram of adipose tissue in the exposed men and much lower levels in the control subjects. Their highest control level coincided with the lowest value in a heavily exposed subject. The range of levels observed by Gross et al in their exposed men is nearly identical to ours, although their samples were taken approximately ten years after exposure while ours were taken after 15 to 20 years, suggesting slow excretion. Unfortunately, there are no data that allow us to compare exposures between their subjects and ours, so a more detailed comparison of the TCDD levels is impossible.

Nygren et al,[illegible] in addition, have reported an adipose tissue value of 100 pg/g in a German chemical worker whose exposure occurred in a factory accident in 1953 and who had had no known subsequent exposure. A biopsy sample of his tissue was taken in 1984, 31 years later. Schecter and Ryan[illegible] and Rappe et al,[illegible] studying other workers from the same accident, found similar levels.

The only published estimate of the

Agent Orange exposure that might yield a given tissue level of TCDD after a ten-year period is that of Weerasinghe and Gross. They based their estimates on a one-year half-life from primate data, on 100% absorption of the applied dose, and on daily exposure for an entire year.

The studies cited previously herein suggest that TCDD has a longer half-life in humans than in rodents or perhaps primates. However, there has been little direct quantitative work on either half-life itself or on the question of whether elimination over a long time is, in fact, a first-order process. Poiger and Schlatter provided the first direct human half-life measurement. Poiger consumed a small amount of radiolabeled 2,3,7,8-TCDD and monitored its excretion, finding a half-life of approximately five years. A person who was exposed in 1966 and found in 1986 to carry 50 pg/g, which is close to the average (41.7 pg/g, Table 2) in the exposed group, would thus have had an adipose or blood fat burden of 800 pg/g immediately after exposure.

More recently, Pirkle et al have reported blood measurements in Air Force veterans involved in herbicide spraying. Samples drawn in 1987 were compared with samples drawn in 1982 and yielded a half-life corrected for background of 7.1 years. Using this number, back calculation for a person carrying 50 pg/g in 1986 would yield 350 pg/g as the body burden in 1966.

All these calculations, including those of Weerasinghe and Gross, assume, of course, that long-term elimination is governed by a single first-order process. Although the data of Poiger and Schlatter are consistent with first-order kinetics, their experiment ran for only a few years. The question remains open for long-term excretion.

Adipose tissue and blood levels are highly correlated (Figs 3 and 4), making it likely that blood sampling will ultimately replace the fat biopsy in tests of body burden. This is the progression that was followed for measurements of human polychlorinated biphenyl levels, the desire to replace invasive procedures by less drastic methods being the motivating factor in both cases. While we are optimistic that blood measurements will become the norm in the near future, we caution that a few unanswered questions remain. How essential is fasting before sampling? The Red Cross recommends against even a 12-hour fast before blood donation, a precaution that is aimed at avoiding untoward side effects on the donor. This, however, does not speak to the question of the effect of fasting on the blood level

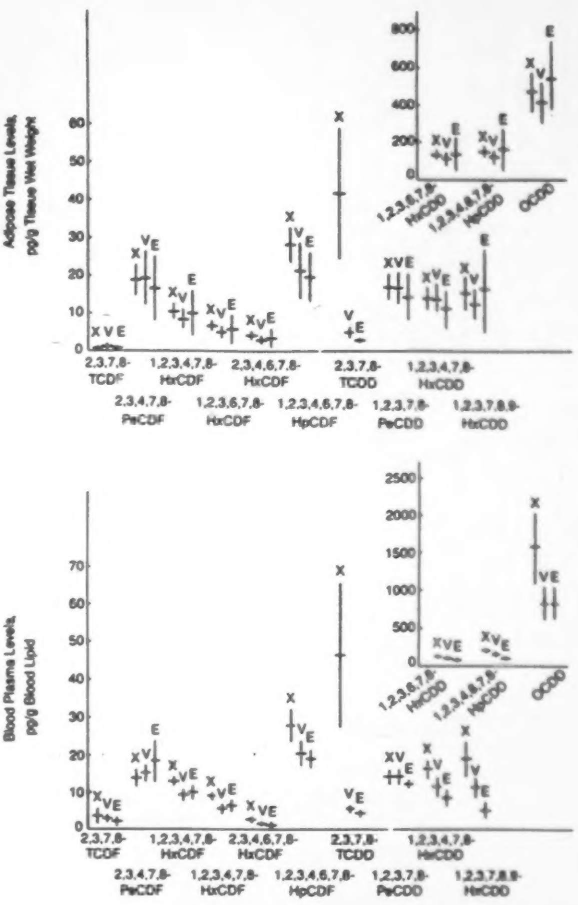

Fig 2.—Mean ± SEM for all 13 congeners found in adipose tissue (top) and blood plasma (bottom). Insets contain three compounds graphed with an ordinate that differs from that of other ten compounds. X indicates exposed subjects (ten); V, Vietnam control subjects (ten); E, era control subjects (seven); HxCDD, hexachlorodibenzo-p-dioxin; HpCDD, heptachlorodibenzo-p-dioxin; OCDD, octachlorodibenzo-p-dioxin; TCDF, tetrachlorodibenzofuran; PeCDF, pentachlorodibenzofuran; HxCDF, hexachlorodibenzofuran; HpCDF, heptachlorodibenzofuran; TCDD, tetrachlorodibenzo-p-dioxin; and PeCDD, pentachlorodibenzo-p-dioxin.

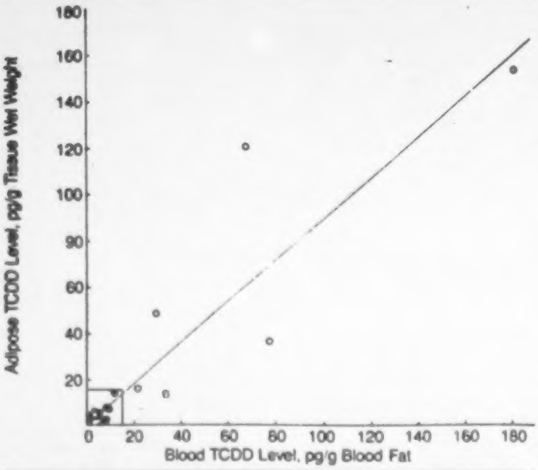

Fig 3.—Comparison of blood fat with adipose tissue levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Least squares regression line is drawn. Box near origin is drawn at 15 pg/g on both axes. It contains all 17 control subjects (closed circles), some atop one another, and three of nine exposed men (open circles) for whom comparison is possible.

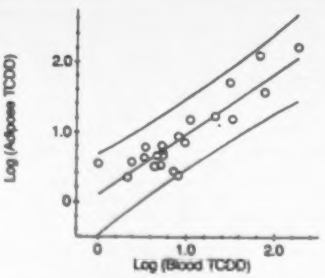

Fig 4.—Regression of adipose tissue on blood fat levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after logarithmic transformation of both axes. Least squares line (middle line) and 95% confidence limits (top and bottom lines) are shown. Plot contains 22 of 26 points from Fig 3 but with no distinction between exposed men and control subjects. Points indicate blood and adipose tissue samples from all men for whom comparison was possible and from those whose TCDD levels were greater than 1 pg/g.

of dioxin. In the parallel study of Patterson et al,[illegible] subjects consumed a restricted diet prior to sampling, and the blood-adipose correlation for TCDD was excellent. This does not answer the question, however, of whether fasting changes the blood level; adipose and blood levels could correlate in both situations but with different constants in the logarithmic regression equation given previously herein. A test of the effects of fasting is therefore in progress.

An additional point that should be considered concerns the use of adipose tissue measurements as a kind of "gold standard" for body burdens of lipophilic compounds such as dibenzodioxins. These and similar compounds accumulate in adipose tissue because of their hydrophobicity. It is usually assumed that the larger the overall body burden, the larger will be the amount stored in the fat. This has not been tested adequately. Second, once stored in adipose tissue, toxic compounds may be less likely to cause health problems than material in, for example, the liver or the central nervous system. We are thus left with the question of whether a well-validated blood analysis might, in fact, be a better index of potential health threat than would an adipose tissue measurement, as it is blood rather than fat that circulates to vital organs. Should it turn out, however, that the equilibrium between blood and fat is rapid with respect to the excretion rate, then they would constitute a single-body "compartment," and measurement of either would suffice.

The results support the statement that men with high levels were heavily exposed and can be distinguished from others by both blood and adipose tissue testing. In Fig 3 all six of the men whose 2,3,7,8-TCDD levels exceeded 15 pg/g were in the exposed group; none of the 17 control subjects exceeded that level. It seems reasonable that with further work it will become possible to use blood measurements as an aid in establishing cohorts of exposed and unexposed men for epidemiologic study of health effects, although we recommend strongly against the use of such measurements as the sole basis for classification (see later herein). In using body burden data, one may prefer to be conservative and set a cutoff for a designation of heavy exposure somewhat above 15 pg/g, but it is clear that an acceptable value can be established. Using 15 pg/g gives a specificity (true negatives/all unexposed) of 100% and a sensitivity (true positives/all exposed) of 70%.

In Fig 3 three of the 20 points within the box bounded by 15 pg/g are from exposed men. The probability that a person whose level falls below this might be heavily exposed is thus 15%. It is of interest, however, that at least two of the three men in the exposed group whose levels are less than 15 pg/g may not have had the heavy exposure that characterizes the rest of the group. One, subject No. 9 in Fig 1, was a ground soldier whose presence in sprayed areas for several months was verified but who was not a spray handler. An accurate knowledge of exposure in such cases is problematic. Another, subject No. 7, found early in his tour that the defoliants made him acutely ill, and after a few missions he ceased to handle them. His exposure could thus have been quite low. Thus, although a low blood or fat level does not necessarily imply the complete absence of exposure, it would seem that heavy exposure does leave sufficient levels of TCDD for the fact of *heavy* exposure to be detected in nearly all cases.

In our experience minimally exposed men can be identified with considerable rigor by a combination of techniques, including questionnaires, military records, interviews in cases where needed, and measurements of TCDD body burden. Although none of these data sources is completely free of error, their combination is far less likely to result in misclassification than any one or two of them. Such a classification procedure should, in our opinion, be used for the exposed population as well, all available data having to be consistent with exposure or the lack of it to include a prospective subject in an epidemiological study. If a less rigorous procedure is to be used, then a carefully constructed validation will be essential.

It is particularly interesting that two of the three men having the highest TCDD levels in this study were not members of Operation Ranch Hand, the Air Force unit that operated the fixed-wing spray aircraft. They were Army chemical corps specialists. We feel that chemical corps personnel constitute a neglected and useful research resource.

Finally, although we can clearly distinguish heavily exposed men from others, the present data do not speak to the question of identifying persons whose exposures are moderate and who constitute the bulk of the population, both military and civilian, who may have been exposed to greater than background levels. We focused this work on heavily exposed men because we were uncertain of detecting TCDD in them in amounts exceeding those found in the control subjects. Having found it, the next step is to examine men of more moderate exposure. Such a study is in progress.

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The men who served as research subjects gave generously of their time and underwent considerable discomfort. For their willingness to take part, we are especially grateful. The cooperation of the US Army/Department of Defense Joint Environmental Support Group and its director, Richard Christian, were much appreciated. We are grateful also for the support and encouragement of Laura Morrow, MD. The critical analysis of Ralph Pagleman, DVM, as well as his support and encouragement are also acknowledged. We appreciate, as well, the cooperation of the Barnert Memorial Hospital Center, Paterson, NJ, whose staff at all levels participated enthusiastically in the care of our research subjects.

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The New Jersey State Commission
The Point Man Project
On Agent Orange

**********MEMORANDUM**********

PLEASE NOTE:

PAGE 16 IS NO LONGER APPLICABLE TO THE "POINTMAN PROJECT" RESEARCH SINCE WE NO LONGER TAKE FAT TISSUE SAMPLES FROM OUR RESEARCH PARTICIPANTS.

WE HAVE FOUND THAT BY TAKING BLOOD SAMPLES WE CAN ACHIEVE RELATIVELY THE SAME RESULTS, THEREFORE OUR PARTICIPANTS NO LONGER HAVE TO UNDERGO ANY KIND OF HOSPITALIZATION.

Since the announcement of our finding that heavily exposed Viet Nam veterans have more dioxin in their bodies than do veterans who were minimally or not exposed, many people have asked us if we could test their blood for dioxin. Unfortunately, we have had to refuse. On behalf of the Agent Orange Commission and the scientific team that conducted this stage of the Pointman Project, we would like to explain why we cannot run extra samples.

Dioxin analyses are not routine procedures. At present there are only two laboratories in the world that have the ability to do them. Both are research laboratories, for the test requires highly trained, skilled research personnel. Neither laboratory can handle the large number of samples that would have to be processed if even a small percentage of those who would like to be tested were to come foreward.

Eventually this situation will improve as more laboratories, including commercial laboratories, learn how to do the analyses, but there, too, people will have to be careful to use labs whose work is accurate or grossly misleading results may be obtained.

For the time being we are adopting another approach to handling large numbers of samples. First, we are trying to set up a sample archiving facility. Because dioxin, like other chemicals, is slowly excreted from the body, the longer the time between exposure and testing, the less the likelihood of finding it. Since it will be several years before the capacity exists to test many samples, we would like to take blood and/or tissue samples now and store them frozen until they can be analyzed. Once an archive is set up, we can then proceed in an orderly and scientifically sound manner to develop analytical facilities.

Another, although less serious, problem is that dioxin tests are expensive, costing approximately $1000 - $1200 each. These costs, by the way, do not involve profit; they are the actual running costs. While some men may be able to pay this amount, and third party insurance may pay for others, costs like these are prohibitive for the majority of people whom testing might benefit.

In the long run - three to five years - there may be a way to circumvent the problem. Several research groups around the world have promising new approaches to testing. They are developing what are called screening assays, which basically give a 'yes' or 'no' answer, i.e. that the person does or does not have more dioxin in them than some pre-set control value. These assays are much less expensive. Samples that come up with 'no' answers need not be examined further. Positive screening results would have to be confirmed by the more elaborate methods that we use now. Since most samples would test negative, the average cost per test would be reduced.

With a sample archive set up and running, the scientific community would have the time to streamline the present procedure and to develop screening and other assay methods to supplement it. You can help here. It costs money, and that can only be obtained if the public wants it to happen. In the interval we hope that you will understand if we restrict our own analyses to samples that will help us understand what is happening and has happened to Viet Nam veterans. In that way we will do the greatest good for the greatest number.

With best wishes,
The New Jersey Agent Orange Commission

The Measurement of Blood Dioxin Levels in Vietnam Veterans Who Were Heavily Exposed to Agent Orange during the War:

A Pilot Project

(Lay language description)

A project of the New Jersey State Agent Orange Commission under the supervision of its scientific subcommittee:

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PREFACE

The protocol for this project is in two parts, an extended lay language description and a detailed technical proposal. This is the lay language description.

A. OBJECTIVES

The principal objective of this work is to determine whether or not 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, or dioxin) can be detected at levels exceeding controls in the blood of a small number of Vietnam veterans who were heavily exposed during the war to the defoliant mixture commonly known as Agent Orange.

The analytical methods to be used are both too difficult and too expensive ever to be used on a large scale for mass screening. For this reason an additional objective is to identify secondary medical indicators for the presence of TCDD, indicators that could be determined inexpensively at regional medical centers.

B. BACKGROUND

For the past several years considerable public attention has been given to the question of whether or not a firm scientific connection exists between exposure of troops to defoliant chemicals during the war in Vietnam and subsequent medical problems either for the veteran or for his children. There is certainly enough evidence to make one suspicious of such a connection. The dioxin that contaminated Agent Orange is one of the most toxic substances known. The symptoms which veterans exhibit, although variable from man to man, when taken together are strikingly similar to those seen in persons exposed to dioxins in industrial accidents.

The persistence of symptoms over many years has also been noted in the medical literature, although there is great variability in the duration of toxic effects. Dioxin is known to be an animal carcinogen, and recent Swedish research, in which persons exposed through industrial and agricultural activity to recurrent low levels of dioxin contaminated materials have an abnormally high incidence of certain cancers, is disturbing. The Swedish work is supported by studies of soft tissue sarcoma incidence in American factory workers. There are enough reports of cancer among veterans to make one concerned that there may be a problem.

Lastly, dioxin is a teratogen. The evidence establishing teratogenicity, however, comes from studies in which the chemical was administered to pregnant female animals and the effect on their offspring noted. For dioxin to be the cause of birth abnormalities in the children of Vietnam veterans would be unusual in that the effect, obviously, is through the father. There is very little work in this area, unfortunately, but one should not dismiss the possibility out of hand simply because it is unusual. Science has produced stranger surprises. Mercury, for example, has been shown to cause chromosome aberrations in men exposed in the course of work to quantities sufficient to produce detectable levels in the blood but insufficient to cause clinical symptoms.

As plausible as all these connections may be, however, and as suspicious as the many instances of illness among veterans may make us, suspicion is not proof. In the absence of clear evidence one way or the other, moreover, public policy concerning Vietnam veterans cannot be formulated, and public discussion becomes increasingly acrimonious and sterile. The need for research work is therefore clear.

C. RATIONALE

Until recently there was no evidence that it would be possible at this late date to detect dioxin in the blood of Vietnam veterans. The 2,3,7,8-TCDD that was present in Agent Orange is biologically active in such small quantities, and it is so many years since exposure ceased that the prospects of a study such as this one appeared dim. Preliminary data presented initially in June, 1981, and published recently, however, show that with advanced techniques (see below) dibenzofurans, which are close chemical relatives of the dioxins (Fig. 1) were detectable at the parts per trillion level (ppt) in blood samples drawn from survivors of the 1968 "Yusho" accident in Japan. In that incident rice oil, used in cooking, became contaminated in the processing factory by the circulating heat exchange fluid that leaked undetected from pin-holes in a heat exchanger used to heat the oil. The heat exchange fluid was a polychlorinated biphenyl (PCB) mixture (see Fig. 1) which, when newly synthesized, was free of significant contamination. Years of heating and cooling in the heat exchanger, however, led to the formation of polychlorinated dibenzofurans (PCDF's) at a level of five parts per million (ppm) in the rice oil. Some 1200 people became severely ill over the spring and summer months of 1968, mostly from the PCB's and partly from the PCDF's. Much of the lingering illness in survivors is thought to be related to the PCDF's.

The toxic effects of PCDF's are very similar to those of the dioxins, with the 2,3,7,8-tetrachloro compounds in each case being the most toxic isomers. The most toxic isomers are also known to be the least readily metabolized isomers and are thus most likely to persist in human tissues.

The level of exposure to PCDF's in the Yusho incident, in addition, is much closer to the Vietnam experience than is the case for factory accidents, from which most of our knowledge of the medical effects of chlorinated multiring aromatic hydrocarbons comes. Depending on the batch and the manufacturer, the defoliants used in Vietnam contained between 0.1 part per million (ppm) and 47 ppm of 2,3,7,8-TCDD with a median of 2 ppm. The 5 ppm value for PCDF's found in Yusho oil is thus of the same order of magnitude as the dioxin contamination of Agent Orange.

Although the primary route of exposure in Vietnam was through the skin, while for Yusho it was by ingestion, the fact that PCDF's could be detected in the blood of Yusho patients twelve years after the cesation of exposure makes it rational to look for dioxin in the blood of the most heavily exposed veterans of Vietnam.

D. PROCEDURE

We plan to locate fifty men who were heavily exposed to Agent Orange during service in Vietnam. By heavy exposure we mean men who handled spray directly and regularly as ground rig spraymen, crews of spray aircraft, and others. Men who simply walked through previously sprayed areas are not, for this purpose, considered to be heavily exposed, nor is present illness to be taken as an indicator of heavy exposure. In all cases the fact of heavy exposure will be verified by a search of military records.

Each heavily exposed veteran will be matched against two controls. Both controls will also be veterans and will be matched to an exposed man for age, race, dates of military service, branch of service, and enlisted _versus_ officer status. One set of controls will be Vietnam veterans whose tour of duty did not entail known herbicide exposure. The other set will not have served in Vietnam[1] and will be presumed to have experienced minimal _military_ exposure to herbicides. All participants will have been questioned in detail to ascertain whether or not other forms of substantial exposure may have occurred. Persons, for example, who have worked in the chemical industry, in certain agricultural occupations, and in other occupations with known potential exposure to dioxin will be excluded for the obvious reason that any dioxin found in them could have arisen from occupational rather than military exposure.[2]

The matching planned here allows a high degree of statistical significance to be achieved with a relatively small number of men. The use cf small numbers of men - fifty cases and one hundred controls - is necessitated, in turn, by the nature of the chemical analysis (see below).

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[1] Nationally only 28% of those who served in the military during the time of the war actually went to Vietnam. The others went to Europe, Japan, Korea, and other places or stayed in the U. S.

[2] We are mindful of the fact that some men who never left the United States were exposed to substantial amounts of defoliant chemicals while in service. Such men will not be used as controls.

It should be emphasized that this is a pilot project rather than a full scale epidemiplogical study. For it to be the latter would require that we identify all those men who fit our definition of heavy exposure as described above. From these we would then have to select randomly a representative group to study. This procedure is impossible for us, for there is no way to identify all those who fit our definition. Our research subjects will be volunteers located through veterans' service organizations and through other channels, with the result that we cannot be absolutely sure that they are representative of all those who are heavily exposed. This in no way detracts from the study's rigor as a pilot project, and we proceed on that basis.

Once the study participants have been selected, each man will be admitted to hospital for three days during which he will receive a thorough physical examination of our design. In addition to the usual features of a physical examination, we shall look for objective signs and symptoms which are attributed to the toxic effects of dioxins and related chlorinated aromatics. Chloracne, for example, arises from exposure to such substances and is widely believed to be a characteristic manifestation of toxicity. Although marked chloracne is unlikely to be present in our subjects, a rigorous dermatological examination will be conducted of all men. Nerve conduction rates, additionally, are known to be depressed by exposure to these chemicals, although other factors such as high alcohol consumption may have this effect, as well, which will necessitate appropriate controls. The examination will also include a battery of physiological and biochemical tests. The choice of these, too, will be based on what we know about the effects of the dioxins. The "T" cell mediated immune response, for example, is known to be inhibited by them.

Lastly, it should be noted that among the toxic effects attributed to chlorinated aromatics such as TCDD are psychopathological changes. These behavior manifestations, unfortunately, resemble those of "post traumatic stress disorder," which is the delayed manifestation of repressed effects arising from the protracted life threatening stresses of combat in Vietnam. To some degree post traumatic stress potentially affects virtually all combat veterans of the war. Faced with a man who has problems, a clinician has, at present, no way of knowing whether those problems arise from post traumatic stress, from chemical poisoning, or from both together. We shall therefore examine each man for psychological attributes. These will later be correlated with the other medical data and with the chemical results in an effort to sort out these two potential sources of psychological change.

With all these data in hand, blood samples will be drawn for dioxin analysis. Dioxin accumulates primarily in fatty tissues and in the liver, with material in the blood being in equilibrium with stored material. All men will therefore fast for twenty-four hours prior to the drawing of blood. This will draw down stored dioxin into the blood, enhancing the prospect of finding it. The analyses will be done in Dr. Christoffer Rappe's laboratory in Umea, Sweden. Dr. Rappe developed the testing procedure for blood and did the Yusho work mentioned above.

Before being sent to Sweden, however, the samples, which will be in identical containers, will be handed over to a third party whom we are calling the Impeccable Referee. This person will be someone with expertise in the field but who is not associated with either the New Jersey group or the Swedish group. He or she will remove our labels from the samples, replacing them with a new set and keeping a key to the label numbers. No one but the Referee will then be able to distinguish samples drawn from cases from those drawn from controls. The analytical chemistry will thus be done in a blind fashion. This unusual step is necessary because of the politically and emotionally charged atmosphere surrounding the Agent Orange question. It is essential to avoid any possible accusation of biasing the results by communicating to the analytical chemists either inadvertently or deliberately which samples are which. The Impeccable Referee will thus be a person of unimpeachable reputation and integrity.

The analytical dioxin results will be returned to the Referee, who will break the code, and the statistical analysis will then proceed. In the analysis we shall look for a correlation between heavy exposure to Agent Orange and blood dioxin levels elevated above those of the controls.

If such a correlation is found, attention will then shift to the development of secondary indicators for the presence of dioxins. The analysis of dioxins at the parts per trillion level requires the use of a specialized high resolution gas chromatograph whose effluent is passed directly into a mass spectrometer. Often more than one kind of mass spectrometry must be done, and the whole operation requires computer control and data analysis. The procedures, including sample work-up, are technically demanding, time consuming, and expensive. The running costs per sample are approximately $1,000, including the costs of synthesizing and purifying individual dioxin isomers for use as instrument calibration standards. One hundred fifty samples (fifty cases and one hundred controls), if received all at once, would occupy Dr. Rappe's laboratory for three solid months, and there are, at best, only a dozen or so laboratories in the world that are capable of doing such analyses. The procedure, therefore, cannot be used to screen many men, and the development of methods that are both ecomonically reasonable and can be used locally will thus be necessary.

We plan three approaches to this problem. In the first we shall use the data from the physical examinations and from the physiological, biochemical and other tests. A cluster analysis will be performed to see if any subset of these data correlate with the presence of dioxin. Should such a cluster be found, the tests in it could be administered locally and relatively inexpensively to identify men who are potentially at risk and whose health should be watched carefully.

In the second we take advantage of the fact that whatever else it may do, dioxin is a liver toxin. The plasma proteins, of which human beings have a great many circulating in the blood, are made in the liver. It is a reasonable hypothesis that even a sub-clinical disturbance of liver metabolism will alter the plasma protein profile. Standard enzyme function tests, unfortunately, examine only a few of these proteins, and it is quite possible that a biological effect would be missed as a result. If all or nearly all of the plasma proteins could be screened, the likelihood of finding an effect would be greatly enhanced.

Fortunately, a technique exists to do this: two dimensional polyacrylamide gel electrophoresis. This is a biochemical procedure that separates proteins initially on the basis of molecular electrical charge and thereafter on the basis of molecular size. One obtains on a rectangular transparent gel slab a two dimensional pattern of spots, each spot corresponding usually to a single protein or, at most, to a few proteins. Each spot is characterized by its position on the gel and by its intensity, which is a measure of the amount of the protein present in the sample.

It is likely that within experimental error most of the spots will be the same for cases and controls. The same cluster analysis that was mentioned above, however, can be applied here to see if any set of spots correlates with dioxin content in the blood.

In addition to serum proteins, we shall examine the proteins in white cells, as it has been found that treatment of these in the laboratory with chemicals having biological effects similar to those of dioxin alters their protein distributions markedly.

The procedure will be validated by a study of laboratory animals which will be treated with known amounts of dioxin.

If the electrophoretic procedure can be developed into a successful test, it will have several advantages. It is relatively rapid, requiring a few days. It uses only a small amount of blood. It could be done in any diagnostic laboratory, and its cost would be relatively low.

The third approach to the development of secondary indicators makes use of dioxin's property as an inducer of mixed function oxidase (MFO) activity. MFO is a system of several enzymes whose function is the metabolism of drugs and poisonous chemicals. It is normally present in very small amounts, if at all, and is made (induced) in response to a toxic chemical entering the body. MFO activity is not narrowly specific to the inducing substrate. Among the substrates that are sufficiently similar in shape to the dioxins to be potential additional substrates in its presence are the polychlorinated biphenyls (PCB's), of which there are 209 possible isomers. Residents of advanced industrial countries all carry body burdens of various PCB isomers in sufficient amounts that their analysis is far easier than that of the dioxins. Our hypothesis, therefore, is that persons exposed to dioxins will have produced a type of MFO activity that differs from the norm, and that one manifestation of the difference will be a reduction in some of the PCB isomers relative to the levels in controls who were not exposed to dioxin. Support for this comes from recent work in which it was found that even thirteen years after exposure to dibenzofurans, survivors of the Yusho accident differ in their PCB isomer distribution from local controls. Two isomers present in the controls are absent in the furan exposed cases. We shall therefore analyze for PCB's as well as for dioxin.

Partly because of the complexity of the study and partly for reasons of expense, we have divided it into two stages. In Stage 1 we shall examine ten exposed men and their associated twenty controls. Stage 2 comprises the remaining forty exposed and eighty controls. If the results of the first stage are promising, we will continue on to the second. If not, the project will be dropped or modified.

In an effort to extract as much useful information from the data as possible, the cluster analyses mentioned above will be carried out with respect to the fact of exposure and with respect to objective signs of illness regardless of the dioxin results.

E. CONCLUDING REMARKS

We are aware that should these experiments succeed two objections may well be raised. The first is that the presence of dioxin does not prove that it is harmful at the levels found. The Veteran's Administration, for example, concedes that all men who served in Vietnam may be presumed exposed. The VA denies, however, that exposure has any deleterious effects at all. The second potential objection is that data obtained on the most heavily exposed men are not necessarily "useful" considering the lesser exposure of most men.

These questions are addressed, at least in part, by other work which the Commission and others have in progress. For the present we respond that one must ask one clear question at a time that is susceptible of an experimental answer. That being done,

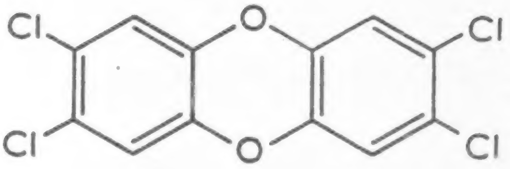
one then formulates another question.

In an interim report to the Governor and the Legislature the Commission ended the section on research activity with the following statement:

> "The Commission is mindful of the intense emotional and political factors that surround its work. We expect that our results will produce controversy regardless of whether or not we can establish a firm link between exposure to defoliants and subsequent medical problems. If the work is to have any value at all, it must withstand searching and possibly hostile scrutiny. The scientific plans must therefore be very carefully laid. The Commission is unanimous in its refusal to do its work any other way."

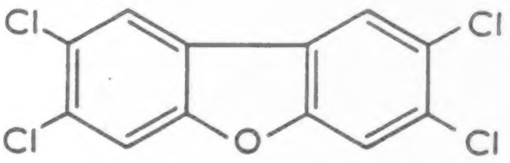
We would appreciate readers' comments, for it is our experience that useful suggestions come not only from scientific colleagues but from interested lay people as well.

FIGURE 1



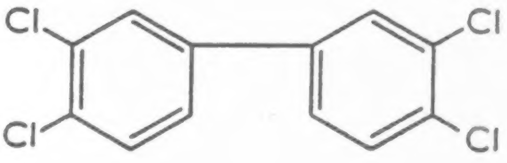
2,3,7,8-tetrachlorodibenzo-p-dioxin

(2,3,7,8-TCDD, "TCDD", "dioxin" - one of 75 possible polychlorinated dibenzodioxins or "PCDD's")



2,3,7,8-tetrachlorodibenzofuran

(2,3,7,8-TCDF, "TCDF" - one of 135 possible polychlorinated dibenzofurans or "PCDF'S")



3,4,3',4'- tetrachlorobiphenyl

(one of 209 possible polychlorinated biphenyls or "PCB's")

O, Cl: Atoms of oxygen and chlorine respectively. Line segments represent chemical bonds. Carbon atoms occur where line segments meet and are not explicitly represented. Parallel line segments represent double bonds. All carbon atoms are involved in four bonds to other atoms. Where only three bonds appear, the fourth is to an atom of hydrogen, which, by convention, is not shown.

Appendix I

The Biopsy of Fat Tissue for Dioxin Analysis

Dioxin accumulates in fat, and we would be more likely to find it if we could analyse fat tissue. Until recently the only way to obtain fat tissue, however, was by abdominal surgery, which we ruled out as too drastic a procedure for research use.

After the study protocol was written, it came to our attention that a much less drastic procedure exists for the removal of subcutaneous fat. It is used by plastic surgeons to contour the body for cosmetic purpose. When adapted for research use, it consists of making a small incision at the crease line between the buttock and upper leg. A thin, hollow steel tube to which suction is applied is inserted under the skin, and the fat is drawn out through the tube.

Although the patient is under general anesthesia, the anesthesia is such that recovery is rapid. The wound does not require stitches but is closed instead by a pressure bandage. There is some discomfort for several days, and vigorous activity is not permitted for a few weeks. A stringent informed consent procedure is followed.

The taking of fat will increase greatly the rigor of our dioxin measurements. By taking both fat and blood from the same people, moreover, we hope to be able to establish the ratio of dioxin in blood to that in fat. If the ratio is constant from person to person, the need to take fat in the future will be greatly diminished, for the amount there will then be obtainable from blood measurements, which are far simpler and less drastic.

The fat samples will also be re-coded by the Impeccable Referee, and the code numbers will not be the same as those used for the blood samples from the same person.

STATEMENT OF MICHAEL GOUGH, PH.D.

CHAIRMAN, VETERANS ADMINISTRATION ADVISORY COMMITTEE ON

HEALTH-RELATED EFFECTS OF HERBICIDES

BEFORE THE SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

COMMITTEE ON VETERANS' AFFAIRS

HOUSE OF REPRESENTATIVES

June 8, 1988

Good morning, Mr. Chairman and members of the Subcommittee. I am pleased to be here again. The last time I appeared before you, I was employed by the Office of Technology Assessment (OTA). I am here today as Chairman of the Veterans Administration (VA) Advisory Committee on Health-Related Effects of Herbicides and as a private citizen concerned about the issues under consideration.

My involvement with the Agent Orange issue began in early 1980, when I was put in charge of OTA's Agent Orange project. I was also OTA liaison to the Agent Orange Working Group (AOWG) and a member of the AOWG's Science Panel. I served in these positions until late 1985. In 1986, after I left the government, my book, Dioxin and Agent Orange: The Facts, was published. I am currently a Senior Fellow in the Center for Risk Management, Resources for the Future, an environmental research organization here in Washington. In December 1987, the Administrator of Veterans Affairs appointed me as the first non-VA Chairman of the VA Advisory Committee on Health-Related Effects of Herbicides. That committee was established by the Administrator in April 1979, when the VA recognized that the Agency lacked adequate expertise to handle the complex issues surrounding the Agent Orange controversy. Establishment of this committee represented one of the earliest attempts to meet the challenges raised by this issue. I personally have not been closely involved with the work of the committee until recently and will limit my remarks to the period of my involvement. I will briefly describe the committee composition, its objectives, the recent meeting, and plans for the future. At the conclusion of my remarks, I will, of course, be pleased to entertain any questions you may have concerning the Advisory Committee or any aspect of the Agent Orange issue.

The committee is composed of 12 individuals with very different backgrounds and perspectives. (A current membership roster is attached). In December 1987, the Administrator reappointed four members and made eight first-time appointments. Three of the members are physicians, two are attorneys, three are employed by major veterans service organizations, two work for or are affiliated with State Agent Orange programs, several are professors, one is a Federal employee (with the Environmental Protection Agency), one was the first Chairperson of the VA Advisory Committee on Women Veterans, and several are researchers. A number of these individuals served in Vietnam. By training and experience, they approach the issues in different ways. I believe the balanced viewpoints and varied perspectives enhance the operation and effectiveness of the committee.

The committee has five broad objectives. The committee is directed to (1) review and make appropriate recommendations relative to the Veterans Administration's programs to assist Vietnam veterans who were exposed to herbicides; such recommendations may concern the VA information dissemination and outreach efforts, essential follow-up activities, and related matters; (2) advise the Administrator on VA Agent Orange-related programs and programs of other federal and state agencies designed to assist veterans exposed to herbicides; and simultaneously, to minimize duplication of VA and other federal programs concerned with the Agent Orange issue; (3) receive and review information from veterans' service organizations regarding services provided by the Veterans Administration to Vietnam veterans concerned about the possible adverse health effects of exposure to herbicides; (4) review and comment on proposals for research on the possible health effects of exposure to herbicides; and (5) serve as a forum for individual veterans to inform the VA of their views on policy issues and on the operation of Agency programs.

On April 15, 1988, the committee met for the 28th time since its establishment in 1979. This was the first meeting since the major membership changes in December 1987 as well as my first meeting. I will briefly summarize the highlights of our proceedings. Draft minutes have been prepared for circulation to the committee members. When that review is complete, I will be happy to provide a copy to this subcommittee.

I was pleased that the Administrator was able to attend the April 15 meeting. His presence served as a concrete manifestation of the continuing importance that the VA places on the Agent Orange issue. General Turnage recognized the committee's expertise and invited its recommendations and suggestions on improving the Agency's program to serve Vietnam veterans. The committee received a number of reports: an overview of Federal research efforts, a discussion of VA studies, a description of

VA's non-research activities related to Agent Orange concerns (Agent Orange Registry program, health care services, publications, conferences, videotapes), a presentation regarding compensation issues, an update on litigation and legal issues, a report on the Veterans' Advisory Committee on Environmental Hazards, a lengthy discussion of various State Agent Orange programs, reports on activities of veterans' service organizations, and a presentation of the draft videotape "Agent Orange: An Update." Time was set aside before the conclusion of the meeting for an "open forum" which allowed the audience to participate in the meeting by bringing concerns and questions to the committee and the Agency.

The committee took three direct actions. Two recommendations will be sent to the Administrator, and VA staff agreed to make an amendment in the VA disability compensation manual. I will discuss that amendment first. Concerns were expressed by committee members and members of the public about the relationship between the disability compensation program and the Agent Orange Registry. In particular, there appeared to be some uncertainty about whether claimants were informed that they should furnish VA with a copy of their Agent Orange examination. The VA Compensation and Pension Service agreed to amend the disability compensation manual to require that claimants be advised to submit a copy of their Agent Orange examination or to identify the VA medical facility where an examination was done so that the VA adjudicator could see it. This change in the manual was agreed to without the need for a formal recommendation to the Administrator.

The committee voted unanimously to make the two formal recommendations to the Administrator. The committee expressed concern about the timeliness of VA communications with Vietnam veterans concerned about the possible adverse health effects of Agent Orange exposure. Specifically, the committee was troubled about the sporadic publication of the "Agent Orange Review" publication, which was most recently released in February 1985 and March 1986. The committee recommended that the Agency move expeditiously to publish and disseminate the Agent Orange Review.

The Advisory Committee also expressed dismay about a possible reduction of Federal benefits to Vietnam veterans who receive funds from the settlement of the class action lawsuit. The committee recommended that the Administrator recommend to Congress that benefits accrued from the Agent Orange litigation settlement with the manufacturers of Agent Orange not be counted against individuals applying for any Federal benefits or services.

Before I close, I would like to make a few comments about another VA advisory committee, the Veterans' Advisory Committee on Environmental Hazards, and its relationship to the committee that I chair. The Environmental Hazards Committee, as I will call it, was established pursuant to Public Law 98-542, the Veterans' Dioxin and Radiation Exposure Compensation Standards Act. That committee consists of four lay members and eleven scientific members. The scientific members serve as the Scientific Council which makes findings and evaluations regarding pertinent scientific studies relating to the possible adverse health effects of dioxin exposure or ionizing radiation. The committee advises the Administrator regarding VA regulations governing the adjudication of veterans' and survivors' compensation claims based upon disabilities or deaths alleged to result from two distinct exposures: exposure of Vietnam veterans to herbicides containing dioxin, and exposure of veterans who participated in atmospheric testing of nuclear weapons or the occupation of Hiroshima or Nagasaki, Japan, to ionizing radiation.

While the scope and functions of the two advisory groups are very different, clearly there are common interests. I attended the most recent meeting of the Environmental Hazards Committee in February and can personally attest to the high caliber of expertise assembled in that committee. I am happy to report that the Administrator recently took the advice of our committee and appointed a member of the Advisory Committee on Health-Related Effects of Herbicides, Mr. Charles F. Conroy, Jr. of the West Virginia Department of Health to serve jointly on the Veterans' Advisory Committee on Environmental Hazards. Mr. Conroy's report at our April meeting demonstrated that he will be an effective liaison between the two groups and enhance the work of each. We have taken one additional step to facilitate and enhance relationships between the two Advisory Committees. The next meeting of the Veterans' Advisory Committee on Environmental Hazards is planned for November 3-4, 1988. I have scheduled our next meeting the day preceding that meeting to promote interaction and communication between members and assist those members and others who wish to attend the meetings of both committees.

Mr. Chairman, that is all I have to report on the Advisory Committee on Health-Related Effects of Herbicides. I will be pleased to respond to any questions you may have concerning the committee or any other aspect of my involvement in the Agent Orange issue during the past eight years. Thank you for the opportunity to once again appear before you to discuss this most complex and difficult issue.

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MEMBERSHIP - 1988

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JUNE 1988

TESTIMONY OF HELLEN GELBAND, SENIOR ANALYST
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U.S. CONGRESS
BEFORE THE HOUSE OF REPRESENTATIVES COMMITTEE ON VETERANS' AFFAIRS
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

CURRENT KNOWLEDGE OF VIETNAM VETERANS' HEALTH AND EXPOSURE TO AGENT ORANGE

June 8, 1988

I am Hellen Gelband, a Senior Analyst at the Office of Technology Assessment (OTA) with primary responsibility for issues related to veterans' health. I am pleased to appear before this subcommittee to offer OTA's perspective on the epidemiologic findings concerning the health of Vietnam veterans, and on the current state of knowledge about exposure to Agent Orange in Vietnam.

Since passage of Public Law 96-151 in 1979, OTA has been one of several groups reviewing and attempting to interpret the evidence concerning potential adverse health effects of Vietnam service, and particularly, of exposure to Agent Orange. We have carried out the statutory responsibilities mandated in PL 96-151 and subsequent laws--reviewing protocols for mandated studies and monitoring their conduct. Over the past eight years we have also, at the request of this committee and of the Senate Veterans' Affairs Committee, formally reviewed the major studies of Vietnam veterans and of chemical and herbicide exposures that have bearing on the Agent Orange issue.

Findings from several important studies of Vietnam veterans' health have become available in the last year. The recently published Vietnam Experience Study, undertaken by the Centers for Disease Control (CDC) under the mandates of PL 96-151 and PL 97-72, is the most prominent. In October 1987, the Air Force reported results of the second round of interviews and physical examinations of the Ranch Hand study (formally, the Air Force Health Study). In 1987, the Veterans Administration (VA) completed a proportionate mortality study of about

50,000 veterans who had died since the end of the Vietnam War. Before I summarize the findings from these and some other studies of herbicide exposure, I would like to recount briefly the research to date on what is known of exposures of Vietnam veterans to Agent Orange.

Exposure to Dioxin-Containing Herbicides in Vietnam

PL 96-151 mandated a study of the long-term health effects of Agent Orange exposure among ground troops in Vietnam. At the time the law was written, the belief was widespread that, given the millions of gallons of Agent Orange sprayed and smaller amounts of other dioxin-containing herbicides, just being in ground combat in Vietnam must have guaranteed significant exposure. When CDC assumed responsibility for the study in 1983, a major concern in the design was whether it would be possible to identify enough unexposed ground troops with whom the exposed could be compared.

In the painstaking process of examining spray records and troop movements, carried out by the U.S. Army and Joint Services Environmental Support Group (ESG), a more complex picture began to emerge. First, the uncertainties inherent in developing an exposure index from military records became clear: while it was possible to define approximately at least one daily position for most military units in Vietnam, some or all of the troops might actually have been many kilometers from that position at various times during the day. It would never be possible to determine the locations of individual men in the field. The records do not contain that level of detail, and the best research cannot compensate for that lack.

If it had been the case that the general areas occupied by troops were constantly sprayed with Agent Orange by Operation Ranch Hand while troops were present, the inability to locate ground troops precisely would be of lesser consequence. But, in fact, spraying was not constant, as the defoliation caused by a single spray or series of sprays lasted many months, and it was rare for troops to be sprayed directly. While the heavily-sprayed areas may have had many separate applications, many areas were sprayed far less frequently. It appears, therefore, that direct exposure during or shortly after Ranch Hand spraying would have been relatively rare among ground troops. Whether significant exposure could occur by being in an area days, weeks, or months after spraying was unknown, and still is, to some extent. However, based on the amount of spray that was likely to have reached the ground, and on what is known of the environmental fate of the herbicide components, including dioxin, it appeared unlikely that significant exposure would have occurred in that way. The remaining uncertainty could not be resolved through more records research, however.

With exposures to Ranch Hand spraying lower than expected, it became important to seek information about non-Ranch Hand uses of Agent Orange to which ground troops might have been exposed. It is known that herbicides were sprayed around base perimeters by Army helicopters, by truck-mounted sprayers, and by men with backpack sprayers, and riverbanks were sprayed from boats. Though these activities accounted for only a small percentage of the total Agent Orange used, it was possible that they resulted in more direct exposures to ground troops than did Ranch Hand sprays. The ESG documented large numbers of these other sprays, but many were not recorded anywhere, and individual sprayers were not always identified in company records.

Many uncertainties remained, but a picture began to come into focus. The best evidence suggested not ubiquitous exposure, but possibly a relatively small number of men with significant exposure. In addition to the clearly exposed Ranch Hands and chemical corpsmen, there were undoubtedly others who had sprayed base perimeters or who had directly handled herbicides in other ways. Some bystanders were probably exposed directly during these operations. Even knowing that contact with Agent Orange occurred, however, it was impossible to define what might constitute a "significant" exposure.

CDC was then confronted with the apparent infeasibility of using military records alone to identify a large group of ground troops with unequivocal Agent Orange exposure, as well as with doubt that a large percentage of ground troops had had significant exposure. To verify the suspected lack of correlation of military records-based exposure estimates with actual exposures, and to learn about relative levels of exposure, CDC undertook its "Comparison of Serum Levels of 2,3,7,8-TCDD With Indirect Estimates of Agent Orange Exposure in Vietnam Veterans," referred to as the "validation study." This study capitalized on new technology to measure dioxin levels in blood serum, which appears to be a reliable indicator of current dioxin body burden, and which, at least at the group level, correlates with heavy past exposures, even many years earlier.

The validation study showed no significant differences between Vietnam veterans and non-Vietnam veterans in average dioxin levels and in the distribution of levels. In both groups, the levels are generally within the "background" range expected in the U.S. population. The rankings resulting from five different methods of classifying exposure used within the Vietnam veteran group were not mirrored in gradations of dioxin levels: for each method, men classified as likely to have had higher exposures did not have higher dioxin levels. Two out of 573 Vietnam veterans with completed tests had dioxin levels of 25 and 45 parts per trillion (ppt), somewhat above the level of 20 ppt that CDC has estimated as the upper limit of "background." Neither of these individuals had a "high" exposure ranking. None of the 88 tested non-Vietnam veterans had a level above 20 ppt, the highest being measured at 15 ppt.

In contrast to the ground troops tested, a group of 30 Ranch Handers with known direct exposure to Agent Orange during the same time period in which the ground troops served, had much higher levels. About half of them had levels greater than 100 ppt, and several were above 300 ppt. The recent New Jersey Agent Orange Commission study also found persistent high levels in men who had handled herbicides.

Information about the biological half-life of dioxin, a measure of persistence in the body, was gathered in conjunction with the validation study. In the half-life study, the 1982 dioxin blood levels of a group of Ranch Handers were compared with their levels in 1987. The rate of decline of dioxin blood levels was calculated based on the difference between the two samples. This study was possible because the Ranch Hand investigators had stored small samples of blood drawn during the first Ranch Hand Study physical examination in 1982 and were able to call upon selected participants to have blood drawn again in 1987. The men were selected by the Ranch Hand investigators as having had probable "high" Agent Orange exposures, based on their experiences in Vietnam. The study was necessarily limited to Ranch Hands with relatively high exposures. Because only small amounts of blood had been stored in 1982, and because the analytic technology for measuring dioxin levels has lower limits, only men with levels of at least 10 ppt in 1982 were included. There is no information, therefore, about the rate of change in dioxin levels among men whose previous levels were already in the "low background" range.

The median half-life of dioxin determined from the paired Ranch Hand blood samples was 7.1 years. (The half-life calculation was based on the assumption that dioxin clearance from the body follows "first order kinetics," meaning that, for a given period of time, a constant fraction of the dioxin body burden is eliminated. That assumption is supported by data from other sources, mainly animal studies, but no corroboration from the Ranch Hand sample itself of the clearance kinetics during an early period after exposure.) In none of the men was there a high level in the 1982 sample and a very low level in the 1987 sample. Therefore, there is no reason to believe that the ground troops, whose dioxin levels are now quite low, would have had high dioxin body burdens while in Vietnam or more recently.

This is the evidence that exists to date. At least some of the men who handled herbicides regularly were exposed to a degree that they retain elevated levels of dioxin in their bodies. Based on current evidence, it appears that few ground troops have elevated levels of dioxin in their bodies. The ground troops tested may not be representative of all ground troops, but CDC, in its validation study, did attempt to identify men who spent much of their tour of duty in heavily-sprayed areas, who, of the ground troops, should have had the greatest potential for exposure. The general dioxin profile of this group was identical to that of men who had not been in Vietnam. There is, of course, no guarantee that exposure would have to have been so high as to result in a currently elevated body burden for some long-term health effect to result. The lack of elevated levels does diminish the expectation of such a finding, however, and forces greater reliance on the epidemiologic data for inferences about health effects.

This body of information on exposure of ground troops to Agent Orange--the low levels suspected from records and confirmed in the validation study, and the inability to distinguish exposed from non-exposed, caused CDC to recommend cancellation of their proposed Agent Orange study. The Agent Orange Working Group and OTA agreed that the study was not feasible.

Recent Studies of Vietnam Veterans' Health

No simple set of answers will ever be found to questions about the health of Vietnam veterans. No single study will be the key to understanding. Vietnam veterans, while sharing a collective experience, are diverse, with varying pre- and post-Vietnam experiences. Even while in Vietnam, they served in different areas, with differing responsibilities and activities. The studies that have been completed and those under way come at the questions from different angles, from broad sweeps--like the Vietnam Experience Study--to disease-specific targets--like the Selected Cancers Study. Information from all the studies, taken together, should tell us if there are widespread health problems in the Vietnam veteran population, and if specific conditions, which are suspected to be related to aspects of Vietnam service, are occurring more frequently among the veterans. What may be missed are Vietnam-related conditions occurring rarely in the entire veteran population, or conditions occurring in particular subgroups of veterans who had some common, but not widespread, experience. Here are the major findings of studies that have been completed as of mid-1988.

JUNE 1988

Vietnam Experience Study

CDC conducted the Vietnam Experience Study (VES) under the mandates of Public Laws 95-151 and 97-72. When CDC assumed responsibility from the VA for these mandates in 1983, this study was planned as one of three, the other two being the ongoing Selected Cancers Study and the Agent Orange Study (which has been canceled because of infeasibility). The VES was designed to find out if there were widespread health problems of any type affecting the general population of Vietnam veterans, by comparing them with veterans who were similar in other ways, but who did not serve in Southeast Asia. In all, more than 15,000 veterans were interviewed, and more than 4,000 underwent intensive physical and psychological examinations.

Of the thousands of questions and measurements taken, a few key findings of significance emerged. The Vietnam veterans show persistent psychological effects from their wartime experience, notably continued symptoms of post-traumatic stress disorder (PTSD) even 20 years after service. Other psychological and emotional problems are also affecting greater numbers of Vietnam veterans than their non-Vietnam veteran counterparts.

Two physical findings are of concern. First, more Vietnam veterans have experienced high-frequency hearing losses than have non-Vietnam veterans, and this is correlated with their combat experience. Second, and more puzzling, more Vietnam veterans have had difficulty conceiving children and more also have low sperm counts compared with the non-Vietnam veteran comparisons.

An additional finding, one that appears to apply broadly to Vietnam veterans, is heightened concern over their own and their children's health. In interview, many more Vietnam veterans than non-Vietnam veterans reported that they themselves and their children had health problems. When the veterans were examined, however, there were few differences other than those that I have noted. Similarly, when asked about their children, Vietnam veteran fathers reported more problems than the comparison fathers. When actual birth and hospital records were examined, however, there were no differences. Vietnam veterans seem to be more aware of the kinds of health events that may not even be noted or recalled by those without Vietnam in their past.

The "Ranch Hand Study"

The Ranch Hand Study (formally, the Air Force Health Study) was begun by the Air Force in 1978 to determine whether those exposed to Agent Orange in Operation Ranch Hand, the main herbicide-spraying force in Vietnam, were suffering adverse health effects as a consequence. The Ranch Hands were compared with a group of Air Force veterans who also served in Vietnam, but who did not spray herbicides. Differences found between the two groups might be attributable to Agent Orange, to which the Ranch Hands had relatively heavy "occupational" exposure (which was discussed earlier in regard to exposure information). In October 1987, a report of the second round of in-depth interviews and intensive examinations of the Ranch Hand participants, conducted in 1985, was released. The results included the 1985 findings and comparison with results of the first interviews and examinations, conducted in 1982.

Few overall differences overall were found between Ranch Hands and comparisons. One, however, is an excess of skin cancers among Ranch Hands, taking into account the follow-up period from discharge through 1985. The excess results from tumors arising through 1982, with no differences noted in the interval between the first and second examinations. This finding is not entirely explained by the major variables usually associated with these cancers (skin tone and exposure to the sun).

The other area still under investigation is the incidence of adverse birth outcomes. In 1982, the men were asked about the children that they had fathered (and other pregnancies not resulting in live children). Significantly more Ranch Hands reported birth defects and deaths shortly after birth than did the comparisons. A decision was taken by the Air Force investigators to seek full documentation of the approximately 5,000 births to men in the study.

Until the collection and analysis of that information is complete, sometime in late 1989, it is not possible to draw conclusions about possible adverse effects on the reproductive capacity of the Ranch Hands. CDC'S finding in the VES, of higher problem-reporting rates, unsubstantiated by medical records, among Vietnam veteran fathers, should add to the caution with which the events reported by Ranch Hands are interpreted.

The Ranch Hand Study will continue with periodic interviews and examinations for the next 20 years. A new dimension to the exposure assessment is about to be added, with determination of blood dioxin levels in all participants. Samples for this purpose were collected during the 1985 examinations and have been stored, and the Air Force is now making arrangements with CDC to have the analyses completed. Results of analyses using these data will be of potentially great importance to the understanding of Agent Orange exposure and its possible effects on Vietnam veterans, and beyond that, to the larger field of dioxin-related research. It will be the first study of a relatively large group of exposed individuals in whom actual body burden of dioxin will be used as a measure of exposure. By reducing misclassification of exposed and unexposed, the study should have greater power to detect Agent Orange effects, if they exist.

VA Proportionate Mortality Study

In this study, the VA examined the causes of death for about 50,000 Army and Marine veterans, about half of whom served in Vietnam and half of whom served elsewhere during the Vietnam era, who died since their discharge from the service. The most striking findings, consistent with findings in several state mortality studies of veterans, concerned excesses of deaths from external causes--motor vehicle accidents, accidental poisonings (including drug overdoses), and other accidents and injuries. The excesses in each category were a relatively small percentage of the total deaths in those categories, but because those categories contain a large percentage of the deaths occurring to young and early-middle aged men, they represent substantial numbers. Other findings include significantly fewer deaths due to suicide than expected, and, among Marines, a greater number than expected due to homicide.

Two other statistically significant findings from this study have occasioned great concern: larger than expected numbers of deaths from lung cancer and from non-Hodgkins lymphoma (NHL) among Marine Vietnam veterans. In Army veterans, a slight deficit of NHL, though not statistically significant, appeared. No information on exposures of any kind, either from military or civilian life, is available to guide interpretation of this study. There is no a priori reason to believe that the excess is due to Agent Orange, particularly in light of the results for the Army. The Marine finding is based on a total of 35 deaths from NHL among Marines, which represents about twice the proportion of deaths expected from the Vietnam-era Marines. This is not a large number, nor is the result so extreme as to be alarming, particularly as a result of a proportionate mortality study design, which has inherent limitations and can produce spurious results. However, as stated in OTA Director Gibbons' letter of October 23, 1987, to Chairmen Cranston and Montgomery regarding this study, we believe that this finding "should be taken seriously and that follow-up work be done to investigate possible explanations."

We understand that VA has been obtaining information to carry out some additional analyses suggested by OTA and other review groups. In our view, however, the most important piece of information will come from the NHL portion of CDC's Selected Cancers Study. Information on a wide range of risk factors for NHL will be generated by this study, and it may help put together the fragmentary picture that now exists regarding NHL, occupational exposures to herbicides and other chemicals, and the risks for veterans. While that study will undoubtedly leave many questions unanswered, the information it does produce will be of tremendous value in interpreting what now exists.

The lung cancer finding should be of lesser concern. The finding is based on a total 130 lung cancer deaths, with the excess being 40 to 50. The Army Vietnam veterans showed no excess. Cigarette smoking is the most obvious potential cause of the excess lung cancer deaths.

It would be logical to examine this possibility before searching for less plausible connections. OTA Director Gibbons commented on this in his October 23, 1987, letters to Chairmen Cranston and Montgomery stating that "it is essential that smoking histories be obtained for these cases, and even more importantly, that information about smoking rates of Marines and other servicemen who did and did not serve in Vietnam be gathered." Differences in smoking prevalence between groups are not uncommon. The Ranch Hand study, for example, reports a significantly higher smoking rate in the Ranch Handers than in the comparisons, and the men in both of those groups served in Vietnam.

Summary

A great deal of progress has been made over the past few years in redefining and clarifying the question of exposure to Agent Orange in Vietnam, and in studying the health of Vietnam veterans. Current efforts, including the continuing Ranch Hand Air Force Health Study and its upcoming serum dioxin measurements, and studies reported to be under way by the New Jersey Agent Orange Commission, will help to further define the bounds of exposure.

Thus far, a relatively small number of psychological and physical effects of Vietnam service have been observed among veterans. At present, none of these appears to be related to Agent Orange. However, the possible effects of Vietnam service and Agent Orange continue to be investigated directly in the nearly complete National Vietnam Veterans Readjustment Study (looking at PTSD), CDC's ongoing Selected Cancers Study, in the continuation of the Ranch Hand Study, and in efforts by state Agent Orange agencies, in particular, New Jersey. In addition, a mandated study of women Vietnam veterans is in the planning stages.

Statement of

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before the

SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
COMMITTEE ON VETERANS AFFAIRS
U.S. HOUSE OF REPRESENTATIVES

on

HEALTH OF VIETNAM VETERANS

STATEMENT OF JOHN F. SOMMER, JR., DIRECTOR
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THE AMERICAN LEGION
BEFORE THE SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
COMMITTEE ON VETERANS AFFAIRS
UNITED STATES HOUSE OF REPRESENTATIVES
JUNE 8, 1988

Mr. Chairman and Members of the Subcommittee:

The American Legion is appreciative that you have scheduled today's hearing on the status, findings and interpretations of scientific research related to the health of Vietnam veterans, with particular emphasis on exposure to Agent Orange.

The American Legion, during a recent hearing before the Senate Veterans Affairs Committee, offered strong support for the establishment of a presumption of service connection for non-Hodgkin's lymphoma based upon exposure to Agent Orange. We felt at that time and continue to believe that there is adequate scientific evidence on which to base such a presumption.

Mr. Chairman, the results of a study entitled "Agricultural Herbicide Use and Risk of Lymphoma and Soft-Tissue Sarcoma", conducted by the National Cancer Institute and the University of Kansas, were published in the Journal of the American Medical Association in September 1986. The population-based case-control study reported that a significant number of farmers were exposed to herbicides containing phenoxyacetic acid, specifically 2,4-dichlorophenoxyacetic acid (2,4-D).

The Kansas study conclusions said that farmers using the herbicides for 20 days per year or more had a six-fold higher rate of the lymphoma than non-farmers. In some cases the rate was as much as eight-fold. The findings showed that human exposure to herbicides containing phenoxyacetic acid - a component of Agent Orange - did not increase the risk of soft-tissue sarcomas and Hodgkin's Disease, but did increase the risk of non-Hodgkin's lymphoma. It should be noted that the herbicides used by most of the farmers in the study were reported not to contain 2,4,5-T, the other important phenoxyherbicide and the source of 2,4,7,8 - TCDD (dioxin) in Agent Orange.

The Kansas study confirms the results of a Swedish case-control study by Hardell et al that suggests an association between herbicides and non-Hodgkin's lymphoma.

Although there are those who will undoubtedly argue that the Kansas study is not sufficient evidence on which to base a presumption of service connection for NHL, The American Legion submits that it must be viewed as adequate because of the lack of conclusive evidence to the contrary, and based upon the manner in which the issue of Agent Orange exposure has been mishandled by the Federal Government.

Mr. Chairman, we realize that the purpose of this hearing is not to consider legislative initiatives, but rather to provide oversight with respect to the issues on which you are receiving testimony. However, there is a measure, H.R. 4479, which we feel is important legislation, and one which needs to be deliberated by the Congress at least by the time the Supreme Court decides the case that is holding up the payments from the Agent Orange product liability litigation.

This bill would exclude payments made to veterans or their survivors under the Agent Orange liability settlement fund from being counted as income when determining eligibility for or entitlement to a veteran's or survivor's pension, or a veteran's medical care under Category A of the means test provisions.

In May 1984, the Agent Orange case was settled for $180 million. The court adopted a distribution plan intended to provide assistance to those members of the class who are in the most difficult circumstances. Under the distribution plan, approximately $150 million of the settlement fund will be allocated to the Agent Orange Veteran Payment Program. The payment program will provide cash awards to certain totally disabled Vietnam veterans and the surviving spouses and children of certain deceased Vietnam veterans.

Veterans who can show exposure to Agent Orange while serving in or near Vietnam from 1961 to 1972 and who are currently suffering from a long-term total disability based upon Social Security rating criteria, which occurred prior to the veteran's 60th birthday and is not caused by trauma, accident, or self-infliction, could receive payments under the settlement.

Spouses or dependent children of deceased veterans who qualify under the above criteria should also receive payments.

Tentatively, veterans could receive a maximum of $12,800 and survivors could receive up to $3,400 under the settlement plan. Veterans or survivors who receive nonservice-connected disability or death pensions would have their pensions reduced on a dollar-for-dollar basis for any payment received under the Agent Orange settlement, and in some cases the entire pension could be discontinued because of this modest income.

H.R. 4479, as mentioned previously, would exclude the payments from being counted as income for pension purposes, or as income with respect to the means test for Veterans Administration medical care. The American Legion fully supports the intent of this proposal. However, we would recommend that the exclusion of income be extended beyond Veterans Administration programs, to include any need-based government assistance program.

Mr. Chairman, although we brought it to the full Committee's attention once before, it bears repeating at this time, that The American Legion is deeply troubled by the Centers for Disease Control's conclusion that the agency cannot find enough Vietnam veterans who were exposed to Agent Orange to do a scientifically valid study of the herbicide's effects on humans.

We are troubled by CDC's conclusion for several reasons. But first, may we digress a moment and mention that about twenty months ago, The American Legion expressed concern about the fact that the Agent Orange study mandated by PL 96-151, which had been taken over by CDC, had become mired in major administrative and methodological problems that had forced the study to a standstill. We stated then that in mid-1985 the Agent Orange study began to deteriorate. There were several changes in the position of study director. CDC began working outside of the originally approved study protocol, which resulted in the Office of Technology Assessment recommending that the study be delayed until a revised protocol was developed and approved, to include an acceptable exposure assessment method. As was stated to the Committee on September 24, 1986, The American Legion was seriously concerned about the status of the CDC Agent Orange study.

It was no surprise to us then, that after conducting a pilot study of its own design, CDC has concluded that the study cannot be done. We also voiced concern about the composition of the study population almost two years ago. Among the veterans eliminated from consideration were those who served more than one tour in Vietnam, those who served in a particular unit for less than 180 days, those who were above the rank of E-5, those who transferred from one unit to another during their tour, and any veteran who served any number of days before or after the proposed study window (January 1967-December 1968). These constraints may appear to be trivial to some, but they eliminated thousands of veterans, many of whom were no doubt heavily exposed to Agent Orange. In fact, it is reported that 83 percent of the original study subjects were disqualified based on criteria set forth by CDC.

The United States sprayed more than 12 million gallons of Agent Orange over a country that is smaller than the State of New Jersey. Therefore, we feel it absurd for CDC officials to state that they cannot find enough people to study. It is unfortunate that CDC was permitted to develop a study that was destined to fail.

The American Legion is mandated to take any and all steps necessary to ensure that the Congressional mandate set forth for an Agent Orange study in PL 96-151 is followed, and that the study is completed as expeditiously as possible.

To that end, we urge the assistance of this Subcommittee and the full Committee in ensuring that the Federal Government fulfills its responsibility to Vietnam veterans and their families by providing answers to the agonizing questions relating to the health effects of exposure to Agent Orange. We are quite aware of and thankful for the interest and concern that has heretofore been expressed by this Subcommittee as problems have developed in this study, and we trust that it will continue.

Mr. Chairman, following a preliminary analysis, we fear that another study conducted by the Centers for Disease Control has been gravely flawed. A report titled "Health Status of Vietnam Veterans", was published in the May 13, 1988 issue of the Journal of the American Medical Association. This is the Vietnam Experience Study, which is the second of three studies that were to be carried out by CDC. This study was mandated by PL 97-72 as an expansion of the scope of the Agent Orange study that was previously mentioned.

Section 401 of PL 97-72 states, in part, as follows: "In conducting such study, the Administrator may expand the scope of the study to include an evaluation of any long-term adverse health effects in humans of such service as such health effects may result from other factors involved in such service, including exposure to other herbicides, chemicals, medications or environmental hazards or conditions. The Administrator may also include in the study an evaluation of the means of detecting and treating adverse health effects found through the study."

Some of the major flaws are briefly highlighted below.

Dilution of Effects through Improper Exposure Definitions

The first flaw is that CDC has deliberately restricted itself to a vaguely defined generalized experience in Vietnam rather than focusing on the specific issues it was mandated to investigate, as set forth previously, which are the physical, chemical and psychological exposures of the Vietnam War.

By defining the "exposure" as a generalized "experience" in Vietnam, CDC has committed a classic flaw in epidemiological study design called the "dilution effect". That is, if the exposure is the general experience, then every person who served in Vietnam is defined, by design, to have been equally exposed to the chemical, physical or psychological hazard. Since approximately only 1 out of every 5 men who served in Vietnam was actually engaged in combat, any possible effects of the exposure will be diluted out when the "normal" experience of the 4 non-exposed men is averaged in. Let us say hypothetically that exposure to combat caused a doubling of the incidence of ulcers among the 20% exposed veterans, the effect would be obscured because 80% of the group being studied would not have been involved in combat and would have a normal background rate of the disease. Only extremely large increases in any disease rate could be discovered and reach statisical significance in a population so diluted.

The dilution effect caused by the inclusion of a majority of veterans with no exposure in the study population is compounded by the deliberate exclusion of some veterans who are likely to show health effects. By design, CDC eliminated veterans with multiple tours of duty in Vietnam, and anyone over the grade of E-5. Although this criteria is not as restrictive as that used in the Agent Orange study, in our opinion it is too restrictive, and damaging to the study.

It is extremely important to keep in mind that by and large, veterans in the 35-45 year old age group should be a healthy group of individuals. They were only admitted into the Armed Forces after passing rigorous physical and psychological examinations. Men in the 35-45 year old age group, as a whole, do not develop many diseases or disorders. Therefore, the prevalence of disease and disability in this group is expected to be low.

A knowledgeable epidemiologist, in our estimation, would try to optimize the chances of observing an effect by including, rather than excluding, the veterans who are most likely to have suffered from the exposures in question. This is one of the most simple applications of the concept of "statistical power", or the statistical ability to observe an effect if one is present.

CDC has thus committed two of the cardinal sins of epidemiology. The agency has diluted the study population through the inclusion of non-exposed veterans, and has decreased the statistical power of the study by eliminating those likely to have been exposed.

Biased Interpretation

In addition to a flawed basic design, CDC compounds its own error with an interpretive bias designed to obscure any results which indicate that a health or well-being problem exists among the veterans. In the analysis of the incidence of PTSD, CDC was forced to separate actual combatants from the other Vietnam-based troops. This is because the clinical definition of PTSD, as defined by the American Psychiatric Association's DSM III, requires a specific exposure to trauma.

When forced to stratify the study population, CDC found that the veterans who were exposed to the trauma of combat are indeed suffering from PTSD and other long-term psychological dysfunction. However, these findings are downplayed by CDC in the general conclusions as follows:

"These psychological problems, however, are not of a magnitude that has resulted in Vietnam veterans having as a group (emphasis added) lower social and economic attainment". This telling phrase is the key to recognizing the inherent bias in analyzing, interpreting and describing the results. It appears that the authors are intent on submerging or obscuring important effects by diluting the subgroups to which they pertain. In other words, in the body of the paper PTSD effects are found, but in the conclusion their importance is purposely downgraded.

There are also some other extremely important points that should be noted. It is our understanding that good research dictates that when an effect is found when the combat experience was taken into consideration, all previous findings should immediately be re-analyzed to see if they too may have been combat dependent. This was not done in the Vietnam Experience Study, nor did CDC differentiate among different levels of combat.

From some of the earlier studies on Vietnam veterans, it has made good scientific sense to hypothesize that the effects of the war would vary, depending upon the levels of combat experienced by the participants. This was one of the major conclusions of the first Congressionally mandated study on Vietnam veterans entitled "Legacies of Vietnam". Research projects since that time, including The American Legion's own Vietnam veterans study, have repeatedly confirmed this conclusion. We are not aware of any other researchers who have dealt with the issues of the Vietnam War and health, who have not taken actual combat into consideration in the basic study design. We do not know whether this was done through a lack of knowledge or a deliberate attempt to limit the possible findings. Whatever the original intent, the end result is that some major findings are missed.

Faulty Interpretation: Calling Positive Effects Negative

Despite flaws in the study design, the CDC data still show positive findings. That is, the Vietnam "experience" did adversely affect the health and well being of some Vietnam veterans. However, each time CDC came up with a positive finding, it was then interpreted to be either negative or wrong.

One example is the PTSD finding mentioned previously. It was a positive and important result - the importance of which was minimized.

Another is that one of the basic assumptions in the design of the study is that veterans are unreliable sources of information about their own health or their past medical history. On this basis, CDC justified an extremely expensive, cumbersome and inefficient study based on personal health examinations of selected veterans. In the May 13 report, CDC compares the health status of veterans obtained from a telephone interview to the health status from a physical examination. Not only were these data statistically indistinguishable, but where differences occurred, the trend was that the veterans had underestimated, rather than overestimated, various indicators of poor health. CDC should have emphasized this as an important finding. Instead the differences were described as recall bias, which undermines some findings of the study.

In the report on the Experience Study, the following "positive" findings were among those obtained in the case of those veterans who served in Vietnam:

a. Nearly double the rate of left ventricular hypertrophy

b. Greater hearing loss

c. Higher levels of GGT, thyroid stimulating hormone and glucose

d. Almost triple the rate of occult stool blood

e. Greater rate of evidence of past hepatitis B infection

f. Two of three sperm analyses significantly abnormal

g. One case of porphyria cutanea tarda, an extremely rare disease associated with herbicide exposure in the past.

None of these findings was discussed in any serious detail in the report. The abstract states that "few objective differences in physical health between the two groups" were found. This appears to be an attempt to minimize the findings.

With respect to another important area, when abnormal skin conditions as a whole were investigated, there was a large and significant increase in the rate of these conditions among those veterans who served in Vietnam. However, CDC, rather than considering this to be at least a highly suggestive, if not a definitive finding, proceeded to classify the skin conditions differently in a second table, which does not appear to be consistent with the first table, and thus turns a positive finding into a nebulous one. This is a particularly disturbing action since skin conditions should be considered, by objective researchers, as particularly important to evaluating toxic herbicide exposures.

Unjustified Refusal to Use Available Exposure Data

Any study of the effects of environmental exposures is limited by the extent to which one can define and quantify the exposure. In general environmental studies of water and air pollution, one is often forced to extrapolate regional or even national exposures from a relatively small number of actual measurements. In occupational environments many researchers must simply substitute number of years in a particular job classification for an actual exposure measure.

In the case of herbicide exposures during the Vietnam War, there is an extraordinarily comprehensive and valuable data set available for quantifying exposures. The U.S. Army and Joint Services Environmental Support Group (ESG) has carefully reviewed virtually all troop movement during the Vietnam War and has reduced this to a codified computer file.

ESG has also developed a Services HERBS tape which contains available records on backpack spraying, helicopter sorties, perimeter spraying, and wheeled vehicle missions. It also contains records of aborts, dumps and leaks that occurred during Operation Ranch Hand spraying missions, plus additional Ranch Hand missions that are not contained in the original HERBS tapes.

The use of this information in determining exposure for both the Agent Orange study which was previously mentioned, and for the Vietnam Experience Study, is vitally important. Although CDC has unilaterally declared that these data are not useful, the agency has not presented sufficient evidence or a logical reason that convinces us that the information contained in the Services HERBS tapes and the HERBS tapes is not useful.

Mr. Chairman, we would like to point out that computerized methods for using this data as an exposure classification system exist, have been published in the peer reviewed scientific literature, and are in use in our own study of Vietnam veterans, as well as in several other studies and applications. This is not to state that one can evaluate precisely the extent of every veteran's exposure to herbicides. Rather, we are emphasizing that such an index is extremely useful for classifying veterans into major exposure probability categories such as not likely to have been exposed; low, medium and high exposure. Such stratification, when available, is of the utmost importance in study design. The failure to utilize an existing system in the CDC studies is a fatal flaw.

In the Agent Orange study, CDC did make an attempt to define exposure to herbicides by using a system which can only be regarded as simplistic for exposure classification. The Exposure Opportunity Index uses only a subjective evaluation of the likelihood of having been exposed to herbicides, without using the computerized spraying records. While chosing this simplistic approach, CDC rejected one of the most carefully developed and extensive records of any environmental exposure to be found anywhere in epidemiologic research.

Mr. Chairman, the responsibility for determining the diseases that may be presumed to be service-connected as a result of Agent Orange exposure was in effect transferred from the Congress to the Veterans Administration with the enactment of PL 98-542, the Veterans Dioxin and Radiation Exposure Compensation Standards Act, enacted on October 24, 1984.

One of the provisions of the Act provided that the Administrator, pursuant to a freestanding provision of law rather than an amendment to title 38, would pay a monthly disability benefit only to certain veterans who served in the Republic of Vietnam, and who incurred either chloracne or porphyria cutanea tarda which became manifest within one year after the date of the veteran's last departure from Vietnam while on active military duty. In the event that a veteran died from either such disease, the Administrator was to pay a monthly death benefit to the veteran's survivors. Benefits were not to be paid in cases where there was affirmative evidence that the disease was not incurred by the veteran during service in Vietnam; where there was affirmative evidence to establish that an intercurrent injury or disease which is a recognized cause of the disease was suffered by the veteran between the date of the veteran's most recent departure from the Republic of Vietnam and the onset of the disease; or if it is determined that evidence in the veteran's service record and other records shows that the veteran was not exposed to dioxin while serving in the Republic of Vietnam during the Vietnam War.

The effective date of benefits established by that Act was October 1, 1984. No benefit was to be paid for a period before that date, and no benefit was to be paid for any period after September 30, 1986.

Mr. Chairman, to the best of our knowledge, no benefit was paid, period.

PL 98-542 also directed VA to promulgate regulations relating to the adjudication of individual claims, to include guidelines, standards and criteria where appropriate. Additionally, the Administrator was to make determinations, based on "sound scientific and medical evidence", after receiving the advice of the Veterans Advisory Committee on Environmental Hazards that was established by the law, as to whether service connection would be granted for chloracne, porphyria cutanea tarda, and soft-tissue sarcoma in the case of veterans exposed to Agent Orange.

In the final regulations the Veterans Administration denied the presumption of service connection for porphyria cutanea tarda and soft-tissue sarcomas, and provided only a three-month presumptive period for the service connection of chloracne.

As of this time, almost four years subsequent to the enactment of this law, no additional conditions have been determined by the Administrator to be presumed to be service-connected based on exposure to Agent Orange.

Given the emotional climate in which this entire matter has been and is now being considered, we believe it would be well for the Federal Government to lean in the direction of liberality while the remaining scientific questions are resolved.

Mr. Chairman, The American Legion is appreciative that you have scheduled hearings on this issue which is of such extreme importance to Vietnam veterans and their families. It is frustrating for those of us who represent Vietnam veterans to try to explain to them, and their families, why little or nothing is being done to determine the long-term health effects of exposure to Agent Orange, or to compensate those who are suffering chronic disabilities which they feel are caused by such exposure.

The American Legion holds fast to the position that it is the responsibility of the United States Government to use every resource available to determine the consequences of exposure to Agent Orange on those veterans who served in the Armed Forces in Vietnam, and then to adequately compensate those who are suffering from diseases and disabilities as a result of that exposure.

Thus far, as far as we are concerned, the government has fallen far short of its responsibility.

Mr. Chairman, that concludes our statement.

STATEMENT OF
DAVID W. GORMAN
ASSISTANT NATIONAL LEGISLATIVE DIRECTOR
FOR MEDICAL AFFAIRS
DISABLED AMERICAN VETERANS
BEFORE THE
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
OF THE
HOUSE COMMITTEE ON VETERANS' AFFAIRS
JUNE 8, 1988

MR. CHAIRMAN AND MEMBERS OF THE SUBCOMMITTEE:

On behalf of the more than 1.1 million members of the Disabled American Veterans and its Ladies' Auxiliary, may I say how very much we appreciate the opportunity to appear here today to comment on the various scientific research relating to exposure to Agent Orange.

As you know, Mr. Chairman, Agent Orange was the most commonly used of several powerful defoliant chemicals sprayed extensively in Southeast Asia during the Vietnam war to deprive the enemy of ground cover and destroy the food supply. The chemical derived its name from the orange stripes that marked the 55 gallon drums in which it was shipped to the war zone.

Military Use of Herbicides and Other Chemicals in South Vietnam

The Department of Defense field tested herbicides in Vietnam as early as 1961 and carried out military herbicide operations from 1962 to 1971. The herbicides were used primarily for (1) defoliating trees and plants to improve observation and (2) destroying food crops of hostile forces. The herbicides used were:

* Herbicide Orange, a 50:50 mixture of 2,4-D and 2,4,5-T, was the most widely used herbicide in Vietnam. The component 2,4,5-T contains a contaminant, TCDD (2,3,7,8 -- tetrachlorodibenzopara-dioxin) which is one of the most toxic chemicals known.

* Herbicide Purple, (a similar mixture of 2,4-D and 2,4,5-T that contained a different form of 2,4,5-T -- that was later replaced by herbicide orange in 1964).

* Herbicide White, a mixture of 2,4-D and Picloram.

* Herbicide Blue, cacodylic acid.

According to military estimates, about 17.7 million gallons of herbicides were sprayed during the 1962 to 1971 time frame. From 1965 to 1971, the military sprayed 10.65 million gallons of Agent Orange, 5.63 million gallons of Agent White and 1.14 million gallons of Agent Blue. The National Academy of Sciences (NAS) estimates that of the 3.6 million acres sprayed, 66% was sprayed once, 22% was sprayed twice, 8% was sprayed three times and 4% of the land area was sprayed four or more times.

Agent Orange was sprayed undiluted in Vietnam at the rate of about three gallons -- containing 12 pounds of 2,4-D and 13.8 pounds of 2,4,5-T -- per acre. Civilian applications of this herbicide's components are usually diluted in oil or water. According to industry officials, the civilian application rate of 2,4,5-T varies from one to four pounds per acre. The military contends that the heavier application used in Vietnam was needed to assure success of the various spraying operations. Military officials also contend that due to the dense jungle canopy, the amount of herbicide penetrating the forest floor would have been similar to those normally applied to brush infested land in the continental United States.

In October 1969, the use of Agent Orange was restricted to areas remote from population. This action was prompted by a National Institutes of Health Report that 2,4,5-T could cause malformations and stillbirths in mice. Research later attributed similar problems to the contaminant TCDD, which is produced during the manufacture of Agent Orange. In April 1970, all use of Agent Orange in Vietnam was suspended. About the same time the Department of Agriculture restricted certain domestic uses of the herbicide because of its possible health hazards.

In 1971, the Air Force was directed to dispose of all remaining stock of Agent Orange. The Air Force has reported that their existing stock of Agent Orange was disposed of at sea by high temperature incineration during 1977.

Previous Legislative Actions

Public Law 96-151. "The Veterans' Health Programs Extension and Improvement Act of 1979," enacted December 20, 1979, mandated the VA to conduct a epidemiological study of the possible adverse health effects of exposure of persons who served in the military in Vietnam to the category of chemicals known as "dioxins" produced during the manufacture of Agent Orange. After approximately two years of virtually no action by the VA, the responsibility for the conduct of the study was transferred to the Centers for Disease Control (CDC) on January 14, 1983. The VA also received the mandate to conduct a comprehensive review and analysis of scientific literature relating to possible adverse health effects from exposure to Agent Orange.

Public Law 97-72. The "Veterans' Health Care, Training and Small Business Loan Act of 1981," enacted November 3, 1981, authorized the VA to provide medical treatment to eligible Vietnam veterans who felt their disability may have been caused by exposure to dioxin or to a toxic substance used in Vietnam. Authority to provide these health care services is scheduled to expire on September 30, 1989.

Public Law 98-542. The "Veterans' Dioxin and Radiation Exposure Compensation Standards Act," enacted October 24, 1984, required the VA to specify standards for deciding compensation claims based upon exposure to Agent Orange or to radiation.

This act also required the VA to establish a Veterans' Advisory Committee on Environmental Hazards. The purpose of the committee is to advise the Administrator on VA regulations, completed and ongoing research and other administrative and legislative initiatives.

Public Law 99-272. The "Consolidated Omnibus Budget Reconciliation Act of 1985," enacted April 7, 1986, mandated the VA to provide for the conduct of an epidemiological study of any long term adverse health effects experienced by women who served in the Armed Forces in Vietnam. The study is to examine health effects, particularly gender-specific health effects, which may have resulted from traumatic experiences during such service, or from exposure to Agent Orange or other herbicides. It is anticipated that a contract for the conduct of this study will be awarded during Fiscal Year 1988.

Combined Federal Activities

In late 1979, the White House established an Interagency Work Group to bring together knowledgeable government scientists to oversee the research, develop areas where scientific study is needed, and report the results as soon as they became available to both the Congress and the general public.

On August 21, 1981, the Agent Orange Working Group (AOWG) was established as part of the Cabinet Council on Human Resources. This action elevated and enlarged the scope of the Interagency Work Group.

On April 11, 1985, the eight Cabinet Councils, including Human Resources were combined into two, the Council on Economic Policy Council and the Council on Domestic Policy to which the AOWG now reports.

The Agent Orange Working Group is under the leadership of the Department of Health and Human Services and includes scientific, legal and policy representatives from that Department, as well as the Departments of Agriculture, Defense, Labor and State, and the Veterans Administration, the Environmental Protection Agency, the White House Office of Science and Technology Policy, Office of Management and Budget and the Office of Technology Assessment.

Mr. Chairman, currently, there are some 70 ongoing research projects and 80 completed research projects dealing with dioxin related research efforts.

Federal Agencies conducting the bulk of current research include the Centers for Disease Control/Center for Environmental Health; Centers for Disease Control/National Institute for Occupational Safety and Health; Department of Defense; National Cancer Institute; National Institute of Environmental Health Services; Environmental Protection Agency; and the Veterans Administration.

Mr. Chairman, in excess of $91 million has been spent thus far on dioxin related research. An additional $122 million has been spent on the 70 ongoing projects to date and a projection of $188 million is estimated to be necessary over the next two decades to complete the current ongoing projects.

Of the 70 ongoing projects, 11 deal directly with Agent Orange issues and the remainder deal with dioxin related issues. However, the 11 Agent Orange projects expend about 78% of the current funding for ongoing projects and are projected to utilize over 93% of the future funding required to complete the total number of ongoing projects.

As you are aware, Mr. Chairman, the Centers for Disease Control (CDC) which has been mandated to conduct the most comprehensive study to date on the health effects of Agent Orange -- the "Agent Orange Study" -- terminated, in September 1987, their contracts under which they had planned to conduct the study. That action effectively cancelled the CDC Agent Orange Study mandated by Public Law 96-151.

CDC's action was predicated upon their determination that it was not possible to identify a large enough number of exposed veterans -- based on military records -- upon which to base a large scale study.

Frankly, Mr. Chairman, we view CDC's decision to totally abort their study incredulous and simply an acknowledgement that their preferred method of conducting such research was not felt feasible.

In our view, efforts to conduct this vital study had preceded at no better than a "snail's pace," since the enactment of Public Law 96-151 in 1979. There is little need here to engage in dialogue of the historical events leading up to the recent announcement cancelling the study. Suffice it to say the best interests of the government and, more importantly, Vietnam veterans have not as yet been served. We are aware of additional efforts being undertaken by other sources that instill some optimism that such a study can in fact be accomplished and done so in a scientifically sound and acceptable manner. (This issue will be addressed later in our testimony.)

Mr. Chairman, it has been over 20 years since the initial spraying of Agent Orange occurred in Vietnam. Since that time untold thousands of veterans and their families have been fearful, confused, frustrated, uninformed and extremely patient while waiting for answers to be found or for action to occur.

They still wait patiently. They wait for their government, their nation, to acknowledge various maladies as possibly being related or unrelated results of their military service and exposure; or they wait for signs that progress is being made in that direction. Further, they wait for some degree of assurance that the government is really doing something to address their concerns in an honest, forthright and meaningful fashion. Many feel this is not occurring.

Mr. Chairman, there appears to be a general consensus that the scientific and medical communities will not, in the foreseeable future, be in a firm position to provide answers to the many questions surrounding the issue of what, if any, adverse health effects result from exposure to Agent Orange.

Clearly, to expect veterans to wait until a large scale epidemiological study and/or long term research is completed is not a realistic response. We view the current process to be slow, tedious and totally inadequate. In our view, the time for affirmative, reasonable and meaningful action has long since arrived.

As you know, Mr. Chairman, since the Agent Orange question first surfaced in the late 1970's this issue has become very emotional, controversial, complex and frustrating.

The many questions raised about the health effects of Agent Orange are scientific ones that require scientific research and analysis to properly answer. Such questions are not prone to receiving quick and easy answers.

The previous decade has produced a myriad of scientific research by many entities relating to dioxin related issues. Also, much research is currently ongoing and will continue for the foreseeable future.

Mr. Chairman, the simple truth is all of these research efforts are clouded with uncertainties and fraught with differing and conflicting interpretations of the scientific data.

A second simple truth is that Congress is, for all practical purposes, unable to clearly resolve the scientific uncertainties and differences inherent in the Agent Orange issue. This is not Congress' charge.

Rather, in our view, the Congress has the ability, in fact the responsibility to chart a course and develop a firm policy of exactly how the federal government will proceed in order to meet the needs of Vietnam veterans who believe they were exposed to Agent Orange and now suffer adverse consequences as a result.

Recommendations

Mr. Chairman, we believe the Subcommittee should carefully consider the following concepts that will, in our view, constitute a reasonable and meaningful approach toward attempting to address the needs of Vietnam veterans.

1) The creation of an "archives" -- the process of maintaining frozen blood samples -- of Vietnam veterans who believe they were exposed to Agent Orange. Samples would be available over the long term for medical analysis as research endeavors may dictate a need.

2) Direct the VA to dedicate sufficient funds for investigator initiated "pilot research studies" of specific components dealing with the Agent Orange issue. (An example of such a "pilot study" may be to develop -- as an alternative to the CDC protocol for the Agent Orange Study -- a feasible and scientifically accepted method of identifying a sufficiently large number of exposed veterans in order to proceed with a large scale study to investigate any adverse health effects of exposure to Agent Orange.)

It seems reasonable that if efforts were undertaken to identify and reach consensual scientific conclusions on individual components of the issue than, a subsequent large scale study may be successfully conducted. This approach differs from the previous theory of proceeding "full speed ahead" to find the many answers surrounding this controversy. In essence, these studies will represent small individual pieces of the puzzle that, when joined together, may represent a clearly visible plan on which to proceed.

3) Direct the Administrator to engage in an active, continual program of outreach services to Vietnam veterans.

Such action would ensure that Vietnam veterans are being provided with current, meaningful information and publications regarding ongoing efforts to address and resolve the many complex issues regarding the health effects of Agent Orange. In the past the VA had printed and furnished, to veterans on the Agent Orange registry, literature and updates regarding the Agent Orange issue. To our knowledge, no such literature has been distributed since March 1986. Obviously, countless thousands of Vietnam veterans and their families are anxious to learn of current efforts being undertaken regarding Agent Orange. It is our opinion that the VA should be the lead agency in disseminating such information. Therefore, we feel that the VA should be directed to provide such outreach and information dissemination services and to do so on a regular basis, i.e. at least twice a year.

4) Direct the VA to conduct a "health-survey" of Vietnam veterans. Participants in such a study could be limited to an already established group of veterans such as veterans enrolled in the Agent Orange Registry. Proceeding with such a survey would permit an analytical review and study of veterans identified as believing they were exposed to herbicides. The VA would be in a position to determine their health status and, importantly, the existence of any commonalities or prevalence of disease(s) or any significant health trends. Additionally, the procedure should become an ongoing effort by the VA at each VA medical facility performing Agent Orange exams.

5) Establish a presumption of service-connection for non-Hodgkins Lymphoma resulting from exposure to Agent Orange.

In our view, a sufficient body of scientific and medical evidence exists to adequately support this measure. As we have indicated previously none of the research is yet precise -- and it may never be -- in establishing a relationship between exposure and subsequent developing disease. However, the weight of the research conducted relating to non-Hodgkins' Lymphoma is sufficient, in our opinion, to tip the balance when considering this particular disability. The most notable research efforts to date include:

* A study of Kansas farm workers which showed a 6 fold increase of non-Hodgkins' Lymphoma in exposed farmers; and

* A VA study "Proportionate Mortality Study of Army and Marine Corps Veterans of the Vietnam War," which showed Marines who served in Vietnam had a 110% higher death rate than expected as a consequence of non-Hodgkins' Lymphoma.

Other significant studies have tended to indicate the relationship between exposure to dioxin and the development of non-Hodgkins' Lymphoma.

Vietnam Experience Study

The Vietnam Experience Study (VES) conducted by the Centers for Disease Control (CDC) was designed to evaluate possible health effects of the general Vietnam experience by comparing the health status of a cohort of veterans who served in Vietnam with a cohort of Vietnam era veterans who served elsewhere (Germany, Korea or the United States).

Criteria for selection of veteran participants included:

* males only
* served in the United States Army
* entered military service between 1965 and 1971 as a draftee or volunteer
* served a single term of enlistment
* discharged from active duty in pay grades E-1 to E-5

The study was conducted with four main components:

* mortality assessment
* telephone interviews
* medical examination/psychological and neuropsychological evaluation
* Reproductive outcomes and child health

The VES used a random sample of 48,513 military records to identify 9,558 Vietnam and 9,023 non-Vietnam veterans qualified for the study. Of these numbers, 234 Vietnam veterans and 34 non-Vietnam veterans died on active duty. Additionally, 246 Vietnam and 200 non-Vietnam veterans died between their release from active military service and December 31, 1983 (mortality study).

For the telephone interview component of the VES 9,078 Vietnam and 8,789 non-Vietnam veterans were determined eligible with a total of 7,924 and 7,364, respectively, successfully interviewed.

A random subsample of 3,317 Vietnam and 3,126 non-Vietnam veterans were invited for a comprehensive health examination, including a psychological evaluation. Of these numbers 2,490 Vietnam and 1,972 non-Vietnam veterans were eventually examined at one specific medical facility.

Mr. Chairman, the mortality assessment revealed total mortality among Vietnam veterans was 17% higher compared to other veterans. This excess mortality mainly occurred during the first five years after discharge and was in the form of motor vehicle accidents, suicide and homicide. After the initial five years, mortality among Vietnam veterans appeared generally similar to that of non-Vietnam veterans. Finally, the overall postservice mortality among Vietnam veterans was similar to that of veterans who returned from combat areas after World War II and Korea.

Of the nearly 18,000 veterans participating in the telephone interview a broad similarity was found in terms of demographic and social characteristics, such as education, income, employment rates and marital status.

Vietnam veterans self-reported more limitations in activities, greater use of prescription drugs and a greater degree of diseases and psychological symptoms.

Mr. Chairman, of the nearly 4,500 medical and psychological evaluations few differences were shown between the two groups of veterans. The most noteworthy differences that were found to be statistically significant were increased incidences of hearing loss, occult blood in the stool, evidence of past infection of hepatitis B, lower sperm concentration and, lower than average proportions of normal sperm cells in Vietnam veterans.

Additionally, Mr. Chairman, in designing the telephone interview and the physical examinations a broad approach was used but emphasized health conditions that have been suggested as being related to prior exposure to herbicides or dioxin (Agent Orange). On examination, however, there were no differences noted between the two groups that implicate Agent Orange as producing any significant adverse health effects.

The psychological evaluations did note a more prevalent incidence of anxiety, depression and alcohol abuse among Vietnam veterans.

The VES also analyzed (in Vietnam veterans) combat related Post-Traumatic Stress Disorder (PTSD). About half of these veterans reported experiencing one or more symptoms related to a traumatic combat event. Of this group, 15% met established diagnostic criteria for PTSD at some time during or after service. In the one month period preceding examination 2% of Vietnam veterans met the full diagnostic criteria for combat related PTSD.

Mr. Chairman, the final component of the VES investigated reproductive outcomes and the health of veterans' children. Noteworthy, is Vietnam veterans self-reported more reproductive and child health outcomes (birth defects) than did non-Vietnam veterans during the telephone interview. However, following CDC's obtaining and reviewing hospital birth records, it was concluded that children of Vietnam veterans were no more likely to have birth defects than were children of non-Vietnam veterans. Although Vietnam veterans reported more problems than non-Vietnam veterans concerning impaired fertility this fact was not confirmed. Conversely, both groups were found to have fathered the same average number of children.

The rates of major, minor and suspected birth defects were, therefore, determined to be similar between the two groups. This finding is felt to be consistent with three previous epidemiologic studies regarding Vietnam veterans' risk for fathering children with birth defects.

Mr. Chairman, the VES clearly identifies that Vietnam veterans are suffering psychological problems more prevalently than their non-Vietnam counterparts. We look forward to the completion and release of the Post-Traumatic Stress Disorder study being done by Research Triangle Institute and now scheduled for completion in October 1988. We feel that study may provide additional insight and analysis in this area.

Clearly, Mr. Chairman, the overall objective results, on a broad basis, should be viewed as good news for Vietnam veterans.

Mortality rates among Vietnam veterans were similar to that of veterans from other combat eras; physical and laboratory examinations revealed few significant differences between the two groups; although more apt to be afflicted with anxiety, depression and alcohol abuse, Vietnam veterans seem to be functioning socially and economically in a similar manner as non-Vietnam veterans, as well as having few differences in terms of neuropsychological performance, neurological findings or other objective measures of physical health, and; reproductive outcomes, as well as birth defects of children were similar between both groups.

Mr. Chairman, this concludes my statement. I want to again thank you and the members of the Subcommittee for permitting us the opportunity to present our views on this timely and vital issue.

STATEMENT OF
JOHN C. BOLLINGER, ASSOCIATE LEGISLATIVE DIRECTOR
PARALYZED VETERANS OF AMERICA
BEFORE THE
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
OF THE
HOUSE COMMITTEE ON VETERANS' AFFAIRS
CONCERNING
MATTERS RELATING TO AGENT ORANGE STUDIES
JUNE 8, 1988

Mr. Chairman and Members of the Subcommittee, it is a privilege for me to be here today to present the views of Paralyzed Veterans of America (PVA) on the status of studies reviewing the potential health effects within the Vietnam veteran population following exposure to herbicides.

Mr. Chairman, the search for clues to discover any potentially adverse health effects of exposure to Agent Orange has been long and convoluted. Millions of dollars have been spent in what can only be described as one of the most extraordinary scientific investigatory efforts involving epidemiology in history. Since the late 1970's, when this effort first began, the investigation has travelled a rocky road. The search faced initial bureaucratic inertia. Subsequently, it has proceeded in an all-out effort to, first, develop the science, and then determine through that science if Vietnam Veterans are, or could in the future be, at risk of suffering life-threatening diseases as a result of exposure to minute quantities of a toxic agent while serving in Southeast Asia some twenty years ago.

At times, the science has not been perfect. Many times the full commitment to pursue that science has not been complete. But we are still much farther down that road than we were ten years ago.

Vietnam veterans and their families, now, have far more answers as to their overall health status than they did before. Still, as this investigation is pursued, we might never find the proper combination of clues which could establish a concrete link between exposure to Agent Orange and certain diseases. That should not stop us from supporting any effort to do so. But in the meantime, we should be cautioned not to endorse or provide compensation for such disabilities unless we can be certain there is a realistic connection between exposure to Agent Orange, and its contaminant dioxin, and that disability. However, PVA does not believe that a connection can currently be found and firmly established between exposure to Agent Orange in Vietnam with disabilities that can be extrapolated to the entire Vietnam veteran population based on the scientific evidence we have reviewed to date. PVA would like to comment on the results of two major studies which, in our view, support this premise.

Last Fall, the VA released the findings of its study entitled "Proportionate Mortality Study of Army and Marine Corps Veterans of the Vietnam War." The study reviewed patterns of mortality among veterans of the Army and Marine Corps who served in Vietnam, and Vietnam era Army and Marine Corp veterans who served in areas other than Southeast Asia.

The study reviewed the records of these personnel to determine the cause of death of 51,421 veterans. Death certificates were used in 96.9 percent of all cases. Forty-nine percent of the group served in Vietnam. Fifty-one percent were Vietnam Era veterans with no "in country" service. The study excluded veterans who did not serve between July 4, 1965, and March 1, 1973; Navy, Air Force and Coast Guard personnel; personnel killed in action, missing in action; those who died of war related injuries; and all women veterans.

The major findings of the study state:

- As a group there appears to be no remarkable difference in the major causes of death between the men who served in Vietnam and veterans who did not serve in Vietnam, with few exceptions.

- Motor vehicle accidents account for 35 percent of deaths.

- Other non-motor vehicle accidents were primarily among Army veterans with 51 percent aircraft accidents.
- Accidental poisonings were elevated among both Army and Marine Corps veterans. In reviewing 100 of these deaths, it was found that 98 percent were due to narcotic overdose, mostly heroin.
- When all malignancies were grouped, Army and Marine Corps Vietnam veterans did not exhibit an excess of cancer when compared to their counterparts who did not serve in Vietnam.
- Although suicide is generally under-reported on death certificates, there appears to be no statistically significant excess of suicide in the Vietnam veteran population vs. their Vietnam Era veteran counterparts.
- Although some studies have suggested that individuals exposed to dioxin could be at increased risk of soft-tissue sarcoma, no excess was seen among Vietnam veterans in this study.
- Marine Corps veterans were seen to have a statistically significant excess of non-Hodgkin's lymphoma when compared to Marines who did not serve in Vietnam. However, this pattern did not appear among Army "in-country" Vietnam veterans (indicating the potential existence of other environmental influences).
- Lung cancer deaths were elevated significantly among Vietnam veteran Marines relative to Marines with no Vietnam experience. But, the Army Vietnam veterans did not demonstrate this higher incidence of death due to lung disease. The study, as well, did not assess if those Marine Corp Vietnam veterans who died of lung cancer had histories of tobacco use. Further review of this correlation has been suggested.

From an epidemiological standpoint, taking both Army and Marine Corps Vietnam veterans as a group and comparing them with equivalent veterans who did not serve in Vietnam, there appears to be no major difference in the mortality experience of either veteran cohort. Only when the main group is broken into subgroups do certain statistical anomalies appear - namely, the NHL and lung cancer deaths among Marine Corps Vietnam veterans only. Both the Office of Technology Assessment (OTA) and other noted scientists who were asked to review this study have questioned the reliability of these findings and suggested that further analysis is necessary before these conclusions should be judged valid.

PVA believes that in breaking the main study group down, the statistical credibility of the entire study is greatly weakened. Attempting to transfer statistical fact from a subgroup (Marine Corps Vietnam Veterans) to imply general liability for incidence of a disease within the study group as a whole does not make a good case in our opinion. Extrapolating these partial findings to assess disability liability for the entire Vietnam veteran population is also a strained conclusion. The study did not review the mortality experience of Air Force, Navy and other in-country Armed Forces personnel. It did not take into account that the Army Vietnam veterans, who served in areas where they could have had potentially higher levels of exposure to Agent Orange, exhibited none of the same statistical significant elevations in causes of mortality.

Perhaps, this is the most consistently troubling aspect of attempting to solve the Agent Orange dilemma. Legislation which would authorize compensation for disabilities associated with exposure to Agent Orange would utilize the VA's definition to quantify veterans exposed to Agent Orange as: "Any veteran who performed active military, naval or air service in the Republic of Vietnam during the Vietnam Era."

This definition admits the current failure of science or historical record to identify exactly who, of the three million men and women who served in Vietnam, were exposed to Agent Orange; when they were exposed; and how much dioxin they were exposed to. The Centers for Disease Control attempted to develop an "exposure index" for its authorized Agent Orange study and admitted that it just can't be done in such a way as to produce an unchallengeable scientific result.

So, on the one hand, we don't really know who was exposed to Agent Orange. Newly developed scientific techniques which can assay dioxin levels by parts - per - billion in blood samples taken from Vietnam veterans, today, could help to trace clues to exposure twenty-five years ago. But who is not to say that those trace elements in a veteran's blood were not absorbed or ingested by exposure to this chemical compound which has been in commercial use and environmentally pervasive in this country, not just Vietnam, for decades. Such tests are not only expensive, costing up to $1,000 per sample, but also stretch the limits of available technology in assaying dioxin levels in the blood by parts per billion.

On the other hand, we have no clear idea of what exposure to dioxin can do to you. We know it is highly toxic. But in what amounts and to what degree and over what period of time and exposure level does it manifest that toxicity in the human body.

In the case of atomic veterans exposed to ionizing radiation, we can identify who was present at a nuclear test. Granted, record keeping on exposure levels was primitive. Monitoring from radiation badges worn by service personnel was inconsistent in recording exposure for all participants. But, from what we know about nuclear physics, if a sailor was within close proximity to a hydrogen bomb detonation, on a particular day, and stayed in that area for a certain period of time following the blast, the chances are that sailor was exposed to radiation. The VA can identify who he is.

Nuclear science, as well, is very clear that such exposure has specific latent effects which can cause identifiable disabilities years later. For this reason, PVA believes that the Congress has acted reasonably and responsibly in authorizing compensation for certain disabilities experienced by atomic veterans. However, we have no similar definitive scientific information on either exposure or cause and effect with regard to Agent Orange and Vietnam veterans.

Vietnam veterans, in a combat situation, over a period of months or years in a tropical environment, were exposed to a multitude of potentially harmful experiences and agents which can carry with them long-term deleterious effects. Severe stress reactions and disorders brought on by combat experiences are well-documented to manifest long-term psychological as well as collateral physical debilitation. Likewise, exposure to a tropical environment brings contact with a host of organisms and parasites completely unfamiliar to western human physiology and medicine - not to mention the insecticides, chemicals, and drugs aimed at combating those agents to keep troops fighting in the field. In general, no matter where it is, war is just not a very healthy place.

There has been a common perception in recent years which cites Agent Orange, and Agent Orange alone, as the culprit responsible for a diverse and extensive list of unexplained disorders among Vietnam veterans. The impetus behind the major studies authorized by the Congress, costing tens of millions of dollars, initially focused only on Agent Orange as the chief villain.

We know that dioxin is not good for you. But we do not know from this study whether or not those Marines who died of non-Hodgkin's lymphoma or lung cancer were even exposed to Agent Orange. But, if we presumed that they were, based on the results of the VA's mortality study, should the Congress only authorize compensation for those specific disabilities for only those Marine Corps veterans who served in Vietnam between July 4, 1965, and March 1, 1973, as the data base in the study demonstrated. Would that be fair?

In PVA's opinion, the only way we can solve this puzzle is to treat Agent Orange as one among many potentially harmful experiences and elements to which Vietnam veterans were potentially exposed. If there are groupings of disabilities, for which compensation is not now authorized, which appear at statistically significant levels for the entire Vietnam veteran population, we should proceed to provide a mechanism to authorize that compensation. In our opinion, that was the impetus behind CDC's Vietnam Experience Study (VES).

Last month, the Centers for Disease Control released the findings of the "Vietnam Experience Study." The study was a multidimensional assessment of the health of Vietnam veterans using a random sample of enlisted men who entered the U.S. Army from 1965 through 1971 - 7,924 Vietnam and 7,364 non-Vietnam veterans participated in a telephone interview; a random subsample of 2,490 Vietnam and 1,972 non-Vietnam veterans also underwent a comprehensive psychological and medical examination. The findings of the study revealed.

- Certain psychological problems were significantly more prevalent among Vietnam veterans than among non-Vietnam veterans. These included depression (4.5% of Vietnam veterans vs. 2.3% of non Vietnam veterans), anxiety (4.9% vs. 3.2%); and alcohol abuse or dependence (13.7% vs. 9.2%); about 15% of Vietnam veterans experienced combat-related post traumatic stress disorder at some time after military service, and 2.2 had the disorder during the month before the examination. Elevation of PTSD in Vietnam veterans showed a strong association with higher levels of combat experiences.

- Still, 15 to 20 years after Army service, Vietnam veterans seemed to be functioning socially and economically in a manner similar to Army veterans who did not serve in Vietnam.

- Vietnam veterans reported current and past health problems more frequently than did non-Vietnam veterans. However, the results of the medical examination showed few current objective differences in physical health between the two groups.

- Perceived exposure to herbicides (a perception that in itself may lead to additional stress) is associated with self-reported adverse health conditions, but is not associated with objective measures of exposure. The higher prevalence of psychological problems among Vietnam veterans does not seem to be related to their being in worse physical health.

- The review of general health experience between the two groups showed no elevation among the Vietnam veterans cohort of disabilities which have been suggested as being related to prior exposure to herbicides or dioxin.

- Vietnam veterans, particularly those who served in tactical military occupational specialties, have higher levels of hearing loss than non-Vietnam veterans.

- Among a subsample of the participants who had semen samples evaluated, Vietnam veterans demonstrated lower sperm counts and a significant decrease in the average proportion of "normal" sperm cells than non-Vietnam veterans. Researchers were unable to determine the reasons for differences in sperm characteristics. However, further analysis showed no difference in fertility histories or birth defects among the two groups.

In summary, PVA believes the results of this study should be encouraging for the vast majority of Vietnam veterans. The study revealed no insidious undercurrent of disabilities undermining the physical health and well-being of the Vietnam veteran population. In fact, the study showed clearly the opposite; that the vast majority of Vietnam veterans have readjusted from military service socially, economically and from a standpoint of general physical health at a level equivalent to their non-Vietnam veteran peers.

We are concerned, however, that the study has once again shown that there is still a lingering higher percentage of psychological disabilities among those veterans who served in Vietnam. As is expected, these disabilities, including post traumatic stress disorder, manifest themselves at higher intensity levels with higher degrees of combat experience.

PVA, as in the past, would like to underscore its support for the maintenance and enhancement of all VA mental health programs for Vietnam veterans. We believe that the VA's inpatient "Combat Unit" program should be expanded to more VA Medical Centers. We believe that the VA's outreach and counseling program, through its Storefront Vet Centers, should remain intact and in place as a valuable resource to provide service. Those veterans who still face difficulties as a result of service in Vietnam are not representative of the entire Vietnam veteran population, but this fact does not make their need any less or diminish the VA's responsibility to meet that need in any way it can and should.

In this connection, one of the most disturbing revelations of the VES study was the demonstrated incidence among Vietnam veterans of a potential anxiety reaction over Agent Orange itself. For many Vietnam veterans the fear of

Agent Orange can be worse than Agent Orange itself. Hopefully, this study, with its positive implications for the health and well-being of the vast majority of Vietnam veterans, can help allay those fears.

Mr. Chairman, all of PVA's members have incurred spinal cord injury, disease, or dysfunction. We see every day, and understand well, the pain and suffering that the long-term consequences of catastrophic, life-threatening disabilities can bring. We know what effects disability can have on individual veterans and their families. We are advocates for the veteran. We strongly believe the government has a definitive obligation to make restitution, and care for those who have served in defense of this nation. We have the deepest concern for those Vietnam veterans who currently suffer debilitating and life-threatening diseases from unknown causes which they suspect to be associated with exposure to Agent Orange. But we know far too well that accident, injury or disease is never anticipated or expected, nor is it often easily explained when it strikes.

The VA is currently authorized by law to provide priority, Category A, inpatient medical services for those veterans. We believe this to be entirely proper as the scientific investigation into the potential effects of exposure to Agent Orange continues. PVA would strongly suggest extending entitlement to Category A outpatient service to these same veterans in the same fashion that this Committee and the Congress approved outpatient entitlement for other veterans in the highest VA eligibility categories through the enactment of H.R. 2616. However, we do not believe that a sufficient connection has been made to provide service-connection for exposure to Agent Orange.

Over the past 15 years, deep concerns have been raised within the entire Vietnam veteran population over the potential long-term consequences of exposure to Agent Orange. Certainly, the purpose of spending millions of dollars in an investigatory effort to study the health status of the Vietnam veteran population and any possible adverse effect of Agent Orange exposure has been to see if compensation is warranted. But in our opinion, this search has also been launched to either allay or confirm the deep concerns thousands of Vietnam veterans who have developed severe anxiety over the potential effects of dioxin.

By far, the vast majority of epidemiological evidence, to date, has shown that Vietnam veterans, as a group, are not at higher risk to certain systemic diseases than those veterans who did not serve in Vietnam. While PVA would support any effort to provide compensation for Vietnam veterans if scientific evidence could confirm that compensation was warranted based on solid and corroborated scientific evidence we would do so. However, proceeding to provide that compensation on the basis that science has failed and that we might never be able to solve this puzzle seems unreasonable to us.

Proceeding with compensation based only on a supposition, no matter how compassionate, does little to allay the concerns of Vietnam veterans, as a group, who seek a definitive answer from their government. It would be easy, and, in our role as veteran's advocates, totally understandable, to support such compensation now. But in doing so, we would only be confirming and promoting suspicion which provides no real answer to the Agent Orange question or the health concerns of Vietnam veterans at all. This could, very well, actually release some of the pressure to continue this important overall search to its conclusion.

VETERANS OF FOREIGN WARS OF THE UNITED STATES

OFFICE OF THE DIRECTOR

STATEMENT OF

GORDON R. THORSON, SPECIAL ASSISTANT
NATIONAL LEGISLATIVE SERVICE
VETERANS OF FOREIGN WARS OF THE UNITED STATES

BEFORE THE

SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
COMMITTEE ON VETERANS' AFFAIRS
UNITED STATES HOUSE OF REPRESENTATIVES

WITH RESPECT TO

THE HEALTH EFFECTS OF AGENT ORANGE EXPOSURE

WASHINGTON, D. C. **JUNE 8, 1988**

MR. CHAIRMAN AND MEMBERS OF THE SUBCOMMITTEE:

The Veterans of Foreign Wars of the United States is made up of over 2.2 million combat veterans. Over 600,000 of our members served this country in Vietnam. Most of these men and women were exposed to the dixoin found in the herbicide called "Agent Orange."

Vietnam veterans have waited over 10 years for answers, from the very government ultimately responsible for exposing them to Agent Orange. But, instead of answers to their questions they have received only more questions to be answered.

- Will exposure to Agent Orange eventually lead to health problems?
- Does dioxin (2,3,7,8,TCDD) cause or contribute to certain disabilities or disease?
- Can the medical and scientific community detect and measure the residuals of Agent Orange within the human system?
- Will Vietnam veterans ever be given an opportunity to be tested

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VFW MEMORIAL BUILDING ● 200 MARYLAND AVENUE, N.E. ● WASHINGTON, D. C. 20002 - 5799 ● AREA CODE 202-543-2239

and know, once and for all, if their body contains the dioxin 2,3,7,8,TCDD?...

So many unanswered questions. Yet, it has been over 10 years since public attention was first focused on the possible health effects or dangers caused by exposure to a deadly toxin found in defoliants used extensively during the Vietnam War. Vietnam veterans have become increasingly aware of the defoliant commonly known as Agent Orange and the toxic nature of the dioxin contained within that substance. Much concern and outrage was expressed way back in 1978 and that same concern and outrage continues to grow. What has been done during all this time to resolve the issue:

- Over $130 million has been spent on research and studies.
- Numerous congressional hearings have been convened.
- Advisory committees have been formed.
- Countless meetings have been conducted.
- Tons of paper covered with statistics and other inconclusive data have been generated.

After reviewing the above activities, we considered what has actually been accomplished that could directly impact individual veterans concerned about their exposure to dioxin and what can be done to resolve their concerns:

- Vietnam veterans now have access to medical treatment for any disability or disease thought to be a result of Agent Orange exposure.
- An Agent Orange physical examination and registry were made available to gather information and help find answers for the many concerns expressed by veterans.
- The medical and scientific community has identified dioxin (2,3,7,8,TCDD) as the Agent Orange contaminate most responsible for

causing adverse health effects.

- The Veterans Administration has officially acknowledged widespread Agent Orange exposure in Vietnam veterans: 3.311a(b) Code of Federal Regulations (CFR) states that: "A veteran who served in the Republic of Vietnam during the Vietnam Era shall be presumed to have been exposed to a herbicide containing dioxin while in Vietnam."
- Service-connected disability has been allowed for chloracne manifested not later than three months from the date of exposure.
- A blood test and a adipose tissue test have been developed and tested that can accurately establish the level of dioxin retained in a human subject.

Through the years the veteran public has been inundated with conflicting reports and seemingly endless delays. Much time and millions of dollars have been expended pursuing perfect understanding, coupled with scientific certainty as to the residual effect of Agent Orange on veterans exposed to its deadly toxin, dioxin.

It is useless to list or even comment further on the tons of paper already generated by the numerous studies and extensive research. The VFW believes that it is time to separate the wheat from the chaff. Individual veterans exposed to Agent Orange want some answers. They want to know what their government intends to do about the physical disabilities they must endure as a result of their exposure to dioxin.

The Veterans of Foreign Wars was among the very first to call for a timely study of the effects of dioxin on veterans. This occurred during the first congressional hearing held on this issue before the Subcommittee on Medical Facilities and Benefits of the House Veterans' Affairs Committee on

October 11, 1978. The VFW also requested medical care for veterans thought to be exposed to Agent Orange and compensation for any disability resulting therefrom. Every August the voting delegates of our organization meet in National Convention and pass resolutions that become the VFW mandate for the following year. Our first Agent Orange resolution was advanced in 1979 and we have since continuously called for a thorough, accurate, yet expeditious resolution of this controversial issue. Our most recent VFW Resolution Number 628 entitled "Herbicide Exposure," calls for liberalizing criteria for the disposition of Herbicide related claims (a copy of Resolution Number 628 is attached).

Numerous legislation has been introduced addressing the Agent Orange issue and most of these bills contain provisions allowing for presumptive disabilities. The VFW supports liberalizing the criteria needed for the disposition of herbicide related disability claims. However, we realize that whenever presumptive disabilities are allowed, the government must set aside the normal rules of evidentiary development in favor of a more compassionate method of establishing service-connected compensation. Good common sense should not also be set aside; if there is substantial evidence clearly showing that the claimant was not disabled as a result of military service, then he shouldn't receive compensation. The VA must be given reasonable guidelines to use while adjudicating these special presumptive allowances, thereby preserving some integrity within the VA compensation system. The burden of proof should be placed on the VA, if they can prove, beyond a reasonable doubt that a claimant's disability is not a result of military service then the VA should be allowed to act on that evidence. The VFW believes that all veterans deserving service-connected compensation, as a result of dioxin exposure, should receive their just entitlement; we could not condone awarding public funds to unqualified beneficiaries.

It is time for the Congress to organize the accumulated results of 10 years of study and apply this knowledge to legislation that would directly impact the individual veteran seeking service-connected compensation.

The VFW believes there is an interim solution available to help alleviate some veteran concerns while continuing to develop a reasonable and responsible method of establishing service-connected compensation on a presumptive basis.

So far the studies have focused on examining aggregate groups of our veteran population and the results reflect only general conclusions. Little has been done to target the individual veteran on a case-by-case basis. We believe there is enough scientifically valid information and evidence available to formulate and apply a plan that could ultimately resolve this issue.

Current regulations, evidence and knowledge allow that:

- Agent Orange used in Vietnam was contaminated with a deadly toxin called dioxin (2,3,7,8,TCDD).
- Dioxin is one of the most toxic chemicals known to man and extraordinarily low dosages can even prove fatal to certain animals.
- Dioxin is known to cause or be associated with certain disabilities.
- The VA acknowledges that all in-country Vietnam veterans are presumed exposed to dioxin while in Vietnam.
- Scientific and technological advancements have recently made it possible to accurately measure the level of dioxin present within the human body by extracting and analyzing blood plasma or adipose tissue.

After considering the above, it appears that the technology for detecting and measuring dioxin is progressing much more rapidly than our ability to understand the biological significance of exposure and retention of dioxin in the human system. It is not how much exposure occurs but how much of the dioxin is retained in the body of the victim. The dose of dioxin received and retained is the important factor and that thought brings us precisely to the major point of this dissertation:

We advocate that any in-country Vietnam veteran who claims residual disability as a result of Agent Orange exposure should be given a blood serum test or an adipose tissue test. If the testing shows an inordinate amount of dioxin (2,3,7,8,TCDD), steps should be taken to evaluate the veteran's disabilities and allow service connection as warranted. If the testing does not show a specified level of dioxin, the veteran should be informed of same and appropriate action taken.

We assert that **DIOXIN** is commonly accepted as the link between Agent Orange exposure and residual disease or disability. Any evaluation of a veteran for presumptive Agent Orange disability should logically include a test to determine the level of dioxin absorbed and retained in his system.

Any legislation advanced by this Committee, that includes Agent Orange presumptions should include:

- A section requiring a blood serum test and/or an adipose tissue test to firmly establish the veteran claimant's retained dosage of dioxin (2,3,7,8,TCDD).
- A section that would contract with a nonprofit scientific organization, to establish exactly what constitutes an unacceptable level of dioxin in the blood or tissue of humans.

- A section that would also contract with a nonprofit scientific organization to establish which disabilities, diseases and ailments can be reasonably and scientifically associated with an unacceptable level of dioxin in the human system. And would allow for ongoing update and reassessment activity to consider additional disabilities, diseases and ailments as scientific and medical knowledge of Agent Orange exposure expands and new technologies are developed.

In conclusion the VFW would like to assert that we are solidly behind a reasonable course of action that would finally allow individual veterans an opportunity to successfully pursue and establish service-connected compensation. Any veteran who believes that he was exposed to Agent Orange should be tested and if:

1) The blood serum or adipose tissue test demonstrates an abnormal level of dioxin, and
2) the veterans military record shows in-country service in Vietnam, and
3) the veteran has a residual presumptive disability that can be attributed to retained dioxin, then...

after considering the above three factors and they prove positive, it is reasonable to award service-connected disability benefits.

We call for and will support legislation designed to give fair, compassionate, and deserving treatment to veterans found suffering from the residual effects of dioxin exposure.

Resolution No. 628

HERBICIDE EXPOSURE

WHEREAS, herbicides, the most common known as "Agent Orange", were utilized in great quantities in Vietnam; and

WHEREAS, many Vietnam veterans were exposed in varying degrees to these toxic defoliants; and

WHEREAS, the Veterans of Foreign Wars is on record supporting the premise that the exposure to herbicides may cause certain health defects; and

WHEREAS, the Centers for Disease Control has been contracted by Congress to conduct studies into the health effects of herbicides on Vietnam veterans; and

WHEREAS, good conscience and equity mandates that Vietnam veterans be given benefit of doubt in the prosecution of their claims until this study is completed; now, therefore

BE IT RESOLVED, by the 88th National Convention of the Veterans of Foreign Wars of the United States, that we continue to endorse and support liberalizing criteria for the disposition of herbicide related claims, to include placing the burden of proof for the award of disability compensation on the U. S. Government rather than on the veteran.

Adopted by the 88th National Convention of the Veterans of Foreign Wars of the United States, held in New Orleans, Louisiana, August 14-21, 1987.

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STATEMENT OF

VIETNAM VETERANS OF AMERICA, INC.

Presented By

MARY R. STOUT
PRESIDENT

and

PAUL S. EGAN
LEGISLATIVE DIRECTOR

before the

HOUSE VETERANS AFFAIRS
SUBCOMMITTEE ON HOSPITALS AND
HEALTH CARE

on

AGENT ORANGE

JUNE 8, 1988

I. INTRODUCTION

Mr. Chairman and members of the Committee, the Vietnam Veterans of America, Inc. (VVA) appreciates this opportunity to present its views on the continuing matter of Agent Orange under consideration at today's hearing. In addition to expressing our views on the issue generally, we will also comment on legislation to provide compensation. Addended to this statement is a statement of scientific views of a Professor of Toxicology at the University of Rochester. We believe these views will add to the body of information useful to this Committee in grappling with this issue. Professor Thomas A. Gasiewicz appeared with the VVA at the hearings held by the Senate Committee on May 12 and, while he is not appearing today, we believe his comments will be useful.

As this Committee knows, the VVA has been deeply involved in this issue for many years. Just as surely, this Committee is also well aware of our dissatisfaction with the VA's responsiveness to veterans deeply troubled by the uncertainty of their current and future health status, given their suspected exposure to toxic herbicides in the Republic of Vietnam.

Apart from what we have come to believe is a clear bias by the VA against awarding compensation for disabilities associated with exposure to dioxin, the history of scientific studies conducted to explicitly ascertain the health effects of dioxin exposure has been checkered at best. Since Congress first directed the VA in 1979 to plan for and conduct an epidemiologic study of persons exposed to herbicides in Vietnam, the VA would have us believe that we are still no closer to being scientifically certain about the effects of exposure than we were nine years ago. Indeed this uncertainty is precisely what the VA seems bent on maintaining in order to withhold compensation in the absence of a strict cause-and-effect relationship between exposure and disease.

In the interim, the study directed in 1979 by P.L. 96-151 was transferred to the Centers for Disease Control (CDC) in 1982. This was done because of the VA's slowness in starting up the study and the agency's initial disavowal of any potential harm from exposure to dioxin. Unfortunately, in 1987 the CDC recommended that the long-awaited exposure study be dropped because of difficulties in determining exactly which veterans were in areas sprayed with herbicide defoliants and at what exposure levels.

In 1981, the Congress passed and the President enacted P.L. 97-72. This legislation offered partial relief to veterans by authorizing health care for diseases that may be associated with dioxin exposure. Since then the VA has given a series of conflicting reports on the numbers of veterans treated for such diseases. We were astounded in 1987 to hear from Dr. Barclay Shepherd that 41,000 inpatients and 1.1 million outpatients had been treated under this law. Even more astounding was the revelation, verified by VA officials, that many Vietnam veteran visits were counted in this number regardless of the veteran noting their concerns of an Agent Orange related illness.

Through a series of correspondence with the VA during the summer of 1987 we were assured that this practice would cease and we were given new numbers. The outpatient visits number was cut by more than one-third yet documents recently received by VVA indicate 37,000 inpatients and 4.1 million outpatients have been treated for Agent Orange related illnesses. We view this count as a public relations effort that probably has little or no validity. Additionally, we are unaware of any analyses of the data accumulated as a result of providing this care. We have to believe that it should have occurred to someone at the VA that evaluating this data could provide important information in ascertaining what, if any, commonality exists in the diseases or disabilities of those veterans treated. This information might have been useful in specifically targeting studies of relationships between dioxin exposure and specific disease.

P.L. 97-72 also expanded the scope of the CDC studies on dioxin exposure by authorizing an experience study in addition to the exposure study. The experience study contained two parts. The first was a mortality study and the second was to be a morbidity study. In neither studies did the CDC determine whether the study subjects were exposed to dioxin. This is because exposure was not a factor in either of these studies.

In 1984, Congress passed the Veterans Dioxin and Radiation Exposure

Compensation Standards Act, P.L. 98-542. The stated purposes of the Act were to ensure that temporary benefits be immediately available to certain veterans and surviving families and that disability compensation be provided on a permanent basis to veterans who were exposed to dioxin and suffer disabilities incurred as a result of military service in Vietnam. The new law contained the finding that some evidence existed to link chloracne, porphyria cutanea tarda and soft tissue sarcoma to dioxin exposure. As a result, Congress ordered the VA to propose new regulations setting forth the criteria for resolving claims relating to exposure to herbicides. The Congress also directed the VA to propose guidelines for VA's evaluation of scientific studies which would be used to determine which diseases could be assumed to result from service in Vietnam. These diseases would then be compensable.

As part of the interim benefits to be provided, disability compensation was to be made available to veterans who served in Vietnam and who developed chloracne or porphyria cutanea tarda within one year of leaving Vietnam. These benefits were to commence between October 1984 and September 1986. Although the VA has acknowledged that several veterans have been afflicted with these conditions, no benefits were ever awarded. Additionally, the VA has admitted that no veteran has ever received any compensation for any disorder claimed to be the result of dioxin exposure. This is perhaps not surprising since the only disease the VA currently acknowledges as possibly resulting from exposure to dioxin is chloracne. This disorder is compensable, but only if its appearance can be documented as having become manifest within three months of leaving Vietnam.

From our perspective over the course of the entire period of debate on this issue, the VA can no longer be trusted. The agency was forced to relinquish responsibility for the original Agent Orange study because of foot-dragging and its widely perceived bias against any connection between exposure and disease. As we discuss below, the VA has failed to fully and properly implement P.L. 98-542. Thus, the agency can no longer be trusted to carry out Congressional intent on this issue.

About all that has shielded the VA from more widespread charges of recalcitrance on this issue than have already been aired is the agency's insistence that there be consensus within the scientific community on a strict cause-and-effect relationship before compensation is warranted. Studies conducted by the federal government have been funded and some have been completed with varying results. Smaller scale studies have been, and continue to be, undertaken by individual states but the results of these too are inconclusive on a strict cause-and-effect relationship.

The VVA strongly believes the studies must continue, but we even more strongly believe that it is improper to await scientific consensus on a strict cause-and-effect relationship before providing disability compensation to veterans with diseases reasonably associated with dioxin exposure. After all of the time that has already passed since the enactment of P.L. 96-151, it seems clear enough to us that scientific consensus within the epidemiologic community on an absolute cause-and-effect relationship will not be reached within the foreseeable future. We therefore believe that it is now time to begin resolving this issue by making the political choices necessary to provide compensation for disabilities presumptively associated with dioxin exposure. This is the approach taken in the Senate and House on April 25 and May 2 of this year, respectively, in approving compensation legislation for ionizing radiation-exposed veterans and it is the approach that must be taken now for dioxin-exposed veterans. Apparently, even the President who signed the radiation legislation into law agrees.

During debate on the atomic veterans legislation, for example, House Veterans Affairs Committee Chairman G.V. (Sonny) Montgomery put the case for making a political decision succinctly by stating that the evidence holding a direct cause-and-effect relationship between radiation exposure and specific disease "will never be available" because "the level of exposure cannot be verified." Why it is so difficult to substitute the term dioxin exposure for the term radiation exposure in connection with affording disability compensation for Agent Orange-exposed veterans is a genuine mystery.

As this committee knows, P.L. 98-542 represented a departure from earlier legislation. It was designed to go further than authorize scientific studies, first by VA and later by the CDC. That law represented a balance between the need for a political decision to be made as a first step in resolving this issue and the VA's expressed opposition to being forced into policies based on political pressure rather than scientific evidence.

Unfortunately, Mr. Chairman, had the VA lived up to its mandate by fulfilling its obligations under the law's Congressional intent, today's hearing might not have been necessary. The VA failed to live up to its mandate, the issue remains unresolved and it is now time to recognize that the VA's objections to taking the political decision-making steps needed to begin resolving this matter must be ignored. Sadly, the VA's historic performance on this issue has rendered irrelevant its input today. The VA and some in this Administration may indeed threaten a veto of compensation legislation just as a veto was threatened against the radiation compensation legislation enacted very recently. Nevertheless, we are prepared to take that risk.

II. THE VVA'S LAWSUIT

The purpose of P.L. 98-542 was "to ensure that Veterans Administration disability compensation is provided to veterans who were exposed during service in the Armed Forces in the Republic of Vietnam to a herbicide containing dioxin... for all disabilities arising after that service that are connected, based on sound scientific and medical evidence, to such service." P.L. 98-542 mandated that the VA promulgate regulations for handling Agent Orange disability compensation claims. The regulations were to be based upon scientific and medical evidence which would be evaluated by an independent advisory committee, composed mostly of scientists. This committee was supposed to review the pertinent scientific studies on the health effects of exposure to dioxin and give advice and recommendations to the VA based on their review of the studies.

Pursuant to the Act, the VA set up the VA's Advisory Committee on Environmental Hazards. The Committee is composed of fifteen members, eleven of which are scientists. It is the role of the Advisory Committee to give advice to the Administrator on whether there is sound scientific or medical evidence indicating a connection between any diseases and exposure to herbicides containing dioxin.

In April 1985, the VA published proposed regulations for compensating veterans for Agent Orange-related diseases. The regulations provided for no disability compensation (except for interim benefits) for any Agent Orange-related disease, except for chloracne if manifested within three months from leaving Vietnam.

In April 1985, the VA's Advisory Committee met for the first time. No scientific studies were reviewed during this meeting. At their next meeting, in June 1985, the Committee reviewed a total of seven (7) studies related to the health effects of dioxin. Even though the VA had been specifically directed to look at whether porphyria cutanea tarda and chloracne were linked to dioxin exposure, the Committee did not review even one study whose specific subject is either of these diseases.

After its review of a grand total of seven studies, the Committee decided that the VA regulations disallowing presumptive service connection status for any disease except for chloracne were based in sound scientific and medical evidence. The VA's regulations were finalized in August 1985. After its June 1985 meeting, the Advisory Committee did not meet again until the spring of 1986. Since that time, the Committee has met approximately twice a year and continues to meet to this day. The Committee has not recommended that any diseases be given presumptive service connected status as related to exposure to dioxin.

The VA's implementation of P.L. 98-542 has been fraught with deficiencies. The VA has failed to comply with the mandates set forth by P.L. 98-542 in several respects. This failure to comply with the Congressional mandates is the subject of a lawsuit that the VVA has brought against the VA. Among the violations of P.L. 98-542 are the following:

(1) As stated above, the VA Advisory Committee, which was charged to review the pertinent scientific studies relating to the health effects of exposure to herbicides containing dioxin, reviewed as a group only a total of seven studies before recommending to the Administrator that the VA should not grant service connected status to veterans for any Agent Orange related

disabilities except for chloracne.

(2) The VA did not provide the Committee with adequate administrative or financial support to conduct a thorough review of the scientific studies. From the beginning, the Committee was set up to meet once or twice a year, not nearly enough time to do a thorough review of the scientific literature. There are over one thousand scientific studies pertaining to the health effects of exposure to dioxin.

(3) Prior to the adoption of the final regulations, the Scientific Council of the Committee did not submit any reports to the VA on the pertinent scientific studies related to dioxin, as it was required to do.

(4) Neither the VA nor the Committee has enunciated a standard of proof by which the studies should be evaluated; that is, there is no clear directive to the Committee as to how much evidence is enough to warrant recommending compensation for a specific disease.

(5) The VA and the Committee are using a strict "cause and effect" test by which to judge whether or not a disease should be granted service connection based on exposure to Agent Orange; that is, unless and until the science shows that dioxin causes a specific disease in humans, compensation will not be granted. This test is being used despite the fact that other diseases have been granted service connection status without proof of a cause and effect (i.e., multiple sclerosis).

(6) The VA Advisory Committee failed to keep accurate and complete minutes of the matters discussed at the meetings.

(7) The VA failed to make evaluations of the findings of scientific studies as required by the Act and to publish such evaluations in the Federal Register.

(8) The VA did not abide by the policy that reasonable doubt be granted in favor of the veteran in promulgating its Agent Orange regulations.

III. DIFFERENCES BETWEEN THE PROCESS USED BY VA AND THE EPA IN ASSESSING THE EFFECTS OF DIOXIN

That the process by which the VA Advisory Committee reviewed the science on the health effects of dioxin was defective becomes glaringly apparent when compared with the process used by the Environmental Protection Agency when it undertook a similar project.

In the early 1980's, the EPA decided to assess the likely adverse health effects in humans, if any, of exposure to dioxin by preparing a health assessment document. Such health assessment documents are often created by the EPA in order to determine safety levels of compounds in the air pursuant to the Clean Air Act.

The EPA's charge was remarkably similar to the charge to the VA Advisory Committee: determine what, if any, are the human health effects of exposure to dioxin. One would assume, therefore, that the method by which both entities attempted to answer this question would be somewhat similar. However, the procedures used by the two groups were as different as night and day.

When the EPA project was started, a thorough and exhaustive literature search was done to locate all of the scientific studies on dioxin. This involved several bibliography searches in libraries and turned up literally thousands of studies. The abstracts for all of these studies were read, and more than seven hundred were chosen as the most pertinent ones, including hundreds of animal studies.

Next, persons were selected who would act as the authors of the health assessment document. The EPA chose as authors persons that were known to be well versed in the dioxin issue. Each author was directed to read all of the seven hundred studies before he or she wrote a particular assigned section of the document.

When all of the authors had read the studies and written the drafts of their sections, the sections were compiled into a draft document. The document then went through peer review. A group of more than thirty scientists from a variety of different fields, including academic, industrial, and political groups, were chosen to act as the peer reviewers. The peer review group examined and discussed the document in detail, until all members were satisfied with the final draft. The EPA then released the final version of the health assessment document in September 1985. The EPA health assessment document concludes that dioxin is a probable human carcinogen.

The EPA's thorough and thoughtful process by which it examined the literature on the human health effects of dioxin is in sharp contrast with the procedures of the VA's Advisory Committee, which was created to do exactly the same thing. For example:

(1) Rather than search the literature for the thousands of scientific studies relating to health effects of dioxin, the VA Advisory Committee went through an ad hoc, informal study selection process.

(2) Instead of reviewing the studies on dioxin and then selecting a meaningful set of the pertinent studies, the VA Advisory Committee reviewed only seven studies before recommending to the VA that its regulations regarding Agent Orange disability compensation were based in sound scientific and medical evidence. Even though the Advisory Committee has now been meeting for nearly three years, it still has not reviewed more than a small fraction of the number of studies reviewed by the EPA.

(3) Rather than review animal studies, which are the only truly controlled experimental studies that examine the biological effects of dioxin, the VA did not give its Advisory Committee any animal studies to review because they were deemed to be not relevant. This is particularly egregious because the few human studies that the Committee has looked at are often denounced as flawed and therefore of little value. For example, most if not all studies of persons exposed to dioxin are unable to accurately determine the extent and amount of exposure, thus putting the results into question. In other words, the Committee will look only at human studies, yet their review of human studies evinces the attitude that no human study will ever be scientifically valid enough to act as a basis for granting compensation. Veterans have been truly put into a Catch-22 situation by the VA whose

bottom line agenda seems to be that compensation will never be granted for any disease.

The VA has had three years to correct these flaws in their procedures. Although there have been some changes since the initiation of VVA's lawsuit, these changes are far too little and too late. The VA and its Advisory Committee should not be put in charge of making the determination regarding Agent Orange compensation. They have proven that they cannot or will not get the job done properly.

IV. RANCH HAND

Last February a new Air Force report criticized some of the 1984 findings in the Ranch Hand study, whose preliminary conclusions have been widely used by opponents of disability compensation for dioxin-exposed veterans to derail a legislative solution. This latest report, written by Dr. Richard A. Albanese, M.D., constitutes an important break from past Ranch Hand reports in two respects. First, it includes a discussion of animal studies in great significance for the first time and second it states, for the first time, that the Ranch Hand study results show pathological effects in several biological areas among Ranch Handers.

A. Background of Ranch Hand

The Ranch Hand study compares the Ranch Handers (approximately 1200 Air Force personnel who were directly involved in the handling and spraying of Agent Orange in Vietnam) to other Air Force personnel who flew in, out of, and around Vietnam but were not part of Operation Ranch Hand. The study looks at the morbidity (illness) and mortality (death) rates of both the control (Ranch Handers) and the comparison (non-Ranch Handers) groups. Prior to February 1988, reports from the Ranch Hand study alleged no real differences between the two groups in either area. Actually, there were a few differences, but these were explained away or were not seen as statistically significant. The Ranch Hand report has until recently been cited as showing that there are no serious ill effects from Agent Orange.

B. Why the Original Ranch Hand Study is Viewed as So Important

The government has praised the Ranch Hand study as the most significant study in the area of determining human health effects of exposure to Agent Orange. Dr. George Lathrop, who was in charge of the Ranch Hand study, has stated that the Ranch Hand study is the most important Agent Orange study because the only group of Vietnam veterans that are known, with a fair degree of certainty, to have been exposed to Agent Orange were the Ranch Handers. Studies of other Vietnam veterans such as ground personnel aren't as good, according to him, because it is difficult to determine who was and who was not exposed. The Ranch Handers, however, were supposed to have been definitely exposed. In addition, the Ranch Handers were presumably exposed to much higher levels of dioxin than were ground troops. Dr. Lathrop has stated that Ranch Handers were exposed to at least a thousand times more Agent Orange than were ground troops. Where these figures come from, however, is unclear.

C. Criticisms of the Study

Without being scientists, it is difficult for VVA officials to describe in any great detail how or why the Ranch Hand study is flawed. However, there are two main criticisms of the study that have been expressed by several scientists we have spoken with.

(1) Exposure Index. There are many factors within the study which make it extremely difficult to measure the exposure to dioxin of the Ranch Handers. All exposure indexes are estimates at best. The February 1988 Update comments on this major flaw.

(2) Power. Since the number of Ranch Handers is so small, it would be very difficult, if not impossible, to use the findings of the study to determine whether there is an increased risk of certain rare cancers and other diseases. The February 1988 Update also comments on this problem.

D. February 1988 Update Overview

The basic mission of the February 1988 Update is to examine the degree to which the Ranch Hand findings are compatible with other experimental (animal) and epidemiologic findings on TCDD.

For each category of biological effect, Dr. Albanese first sets forth the results of some animal studies in that area. For example, in "Reproduction", he describes the results of many animal studies, all of which suggest that dioxin has an adverse reproductive effect. The presentation of the animal data implies a strong suggestion that dioxin does have a toxic effect in that particular area.

Dr. Albanese next describes the Ranch Hand findings in that particular area. However, the Ranch Hand findings are fairly weak by contrast with the animal studies. Dr. Albanese generally omits comment on the significance of the Ranch Hand findings, except to state whether they are "statistically significant". However, he does comment that the Ranch Hand findings may be weak because of the low power and because of the imprecision of the exposure statistics.

E. A Review of the February 1988 Update

1. Introduction

This report reviews findings of the first 1984 morbidity Ranch Hand update and laboratory and other epidemiologic studies in eleven clinical areas. In six of these areas, statistically significant group differences occurred, and in five of these six instances group differences showed Ranch Handers in poorer health than non-Ranch Handers.

2. Methods

Dr. Albanese goes through the study design and then goes into detail about the inference concerning herbicide causation of ill health. Because the Ranch Hand study is of an unplanned environmental exposure type, it does not follow an experimental design. Rather, it is an observational study which by definition contains the flaw that arises from an inability to select out confounding factors, factors that may affect the differences between the two groups.

The exposure index in the Ranch Hand study is mostly guess work. Estimates of herbicide effect, according to Dr. Albanese, "must be viewed with great care due to the possibility of many confounding factors." The Ranch Hand study applies theater-wide spraying to a single individual and assumes all individuals in a job category were equally exposed. It does not take into account hygiene data, which is unavailable, or the possibility that higher exposures occurred in the lower ranks of the Ranch Hand cohort.

The 1988 Update next sets forth in broad terms the physical, laboratory and psychological examinations that the Ranch Hand study participants were put through.

3. Results

i. Morbidity

The baseline morbidity report in the Ranch Hand study had 13 primary clinical chapters. More than 190 clinical variables were tabulated. In this Update only a subset of those variables are discussed, specifically in areas where there is laboratory data available that can be compared with the Ranch Hand findings.

The Ranch Hand study has "virtually no power for detecting relative risks" for rare diseases, but has good power for detecting relative risks for common diseases.

ii. General Health

- Weight Loss

Dr. Albanese sets forth several animal studies that show a weight loss effect from TCDD. The Ranch Hand study shows no statistically significant differences between the Ranch Handers and the comparison group in body weight. Also, there was no relationship between body fat and the exposure index.

- Neoplasia (cancers)

Different animal studies have indicated that TCDD is a carcinogen, a cocarcinogen, and an anti-carcinogen. The Ranch Hand studies show a higher incidence of both skin cancer and systemic cancer among the Ranch Handers.

- Reproduction

Dr. Albanese describes various animal studies, many of which show a reproductive effect in animals exposed to TCDD. Similarly, the Ranch Hand group has a statistically significant increase in birth defects. The Ranch Hand report asserted that birth defects such as minor skin lesions accounted for the birth defects excess in Ranch Handers' children. It also asserted that over-reporting by overly sensitized participants could account for the excess. Dr. Albanese states that these assumptions are no longer necessarily valid. In other words, the excess must be taken more seriously.

- Neurological Findings

Although neurological symptoms have been described in workers following industrial accidents involving TCDD, and animal experiments have also shown neurological changes, there are no statistically significant differences in the Ranch Handers to date.

- Psychological Assessment

Both animal and human studies show that TCDD provokes irritation, anger, fatigue, and or inability to concentrate. The Ranch Hand study showed all Ranch Handers to have more problems with these and other psychological symptoms, including isolation, depression and anxiety. The differences are statistically significant. Those with higher education (and therefore more likely to have been officers) did not suffer psychological symptoms as severe as those with lower education. No data were adjusted for combat stress.

- Hepatic Examination (Liver)

Dioxin has been associated with hepatotoxicity. Several animal and some human studies showing liver effects are discussed. An explanation of the Ranch Hand groups follows the discussion of the studies which states that there are generally no differences between the groups except in a few specific areas.

- Dermatological Findings

TCDD is known to cause chloracne. Sometimes chloracne resolves itself in a short period of time, other times it may persist for years. In the Ranch Hand study, no active cases of chloracne were found in either group.

- Cardiovascular System

There are some animal studies that suggest a cardiovascular effect from TCDD. However, in the Ranch Hand study no statistically significant differences were found except for abnormal pulses which were higher in non-black Ranch Handers. There were no differences between black Ranch Handers and black non-Ranch Handers.

- Immunological Effects

Animal studies show immunological effects from TCDD. The Ranch Hand study showed no statistically significant differences.

- Endocrinological Effects

Animal studies show endocrinological effects from TCDD. The Ranch Handers have both negative and positive effects in this area.

- Mortality

Studies with animals show increased mortality with large doses of TCDD. No animal studies have been done to show the possibility of life abreviation resulting from very low doses of dioxin over an extended period of time. There is no statistically significant difference between the Ranch Handers and non-Ranch Handers for mortality. However, there is a marked difference between officers and enlisted men with higher death rates for enlisted men.

V. CDC MORBIDITY STUDY

The Centers for Disease Control has released the morbidity results of its Vietnam Experience Study. The study was broken down into three parts: a psychological assessment, a physical health assessment, and a reproductive effects assessment.

The psychological assessment results report that Vietnam veterans have an increased prevalence of psychological problems, including anxiety, alcohol abuse, depression, and Post-Traumatic Stress Disorder.

The CDC reports that Vietnam veterans' physical health is generally no worse off than non-Vietnam veterans, except for a couple of areas; specifically hearing loss and low sperm count.

The CDC reproductive effects assessment tells us that Vietnam veterans report more birth defects than non-Vietnam veterans, but that hospital birth records failed to confirm a higher rate of birth defects.

The CDC study is being described as showing that Vietnam veterans basically have no adverse health effects from Agent Orange, and that the only major differences between Vietnam veterans and non-Vietnam veterans is that Vietnam veterans have more psychological problems. However, several aspects of the CDC study should be noted that tend to indicate that the CDC results should not be used to make such sweeping statements about the health effects of Agent Orange.

1. There are still other studies that are ongoing concerning the health

effects of the Vietnam experience and exposure to herbicides containing dioxin. The CDC should be constrained from making statements that this study definitively answers the questions regarding these two issues when there are other important studies by institutions that have not been completed e.g., the CDC itself, the VA and studies associated with various Agent Orange commissions, and studies still under various ongoing institutional research protocols.

2. The CDC study does not examine the effects of exposure to dioxin. Absolutely no attempts were made in this study to evaluate the exposure to Agent Orange suffered by the Vietnam veterans involved. Therefore, no conclusions can be drawn regarding the health effects of exposure to dioxin from the results of this study.

3. The CDC conducted part of its study by doing telephone interviews of Vietnam and non-Vietnam veterans. The veterans' responses were verified by physical examination in only 42% of the cases. Based on these examinations, the CDC concluded that Vietnam veterans self-reported more health problems, but the physical examinations did not verify that they did suffer from more health problems. There is a danger that this conclusion is erroneous because a full 58% of the veterans interviewed were not examined. It is important to note that only 75% of the Vietnam veterans randomly selected to be examined actually participated and only 63% of the non-Vietnam veterans who were selected actually participated. It is possible that veterans who were in poorer health, or had other committments, would not choose to travel to have a three day physical examination, thus skewing the results.

4. Simply because the CDC study does not at this time demonstrate a strong cause and effect relationship between dioxin exposure and current illnesses or pathological findings does not mean that such a relationship does not exist. The authors of the study fail to make this important point.

5. The CDC results released in the JAMA article only address a few select areas. It would be helpful for veterans groups and others to see the results in the full range of areas examined.

6. The authors of the CDC study make the comment that their Agent Orange blood study showed that "few US Army ground troops had been heavily exposed to dioxin-containing herbicides." This is an irresponsible and misleading statement. In the Agent Orange Serology Study conducted by the CDC there were essentially no differences in the blood levels of dioxin in Vietnam veterans who they believed may have been highly exposed, based on examining military records (which have been continuously described as inaccurate), and veterans who they believe were not exposed. The study did not mention that there were several explanations for why the blood levels of dioxin were the same. For example, the military records were too inaccurate and the half life expectations of dioxin could explain why veterans heavily exposed to Agent Orange had lower doixin blood levels than would have been recorded years earlier.

7. The CDC states that only 15% of the Vietnam veterans studied had ever suffered from PTSD and that 2% had experienced the disorder during the month before the examination. These numbers relate only to veterans meeting the full diagnostic criteria for PTSD. It is important to note that much higher percentages of Vietnam veterans had suffered at least some of the symptoms of PTSD. Again the actual examinations conducted were limited.

8. Confirmation of reported birth defects through hospital records carries the potential of missing many birth defects that were not initially recorded on the hospital records. Often, developmental birth defects do not become apparent until weeks, months, or longer after the birth of the child.

9. Even though the tables in the JAMA article show for the most part non-statistically significant differences between the two groups of veterans, the tables still show that Vietnam veterans as a group generally have more health problems. For example, in Table #3 (Cardiorespiratory Conditions Among Examination Participants), Vietnam veterans have a higher rate of conditions in nine of the eleven categories shown.

10. The CDC did not appear to give much weight to the fact that six Vietnam veterans had non-Hodgkins lymphoma vs. only one non-Vietnam veteran. Because three of the cases have not been confirmed yet, the CDC appears to

be saying that these findings are not significant. In light of the fact that several studies have shown a relationship between dioxin and/or Vietnam service and non-Hodgkins lymphoma, we feel that the CDC's attitude toward this finding is inappropriate.

11. It is important to note that the CDC only checked a small, non-random sub-sample of birth records to confirm reported birth defects. It would have been preferable to examine all birth defects to ensure a more accurate result.

VI. HR.4479 AGENT ORANGE SETTLEMENT FUND OFFSET

Recently legislation has been introduced in the House by Representative George J. Hochbrueckner, HR.4479, which serves as a companion bill to legislation introduced last year, S.2011, by Senator George Mitchell. These measures would preclude the VA from counting money received from the Agent Orange Settlement Fund as income when determining eligibility for certain means tested benefits.

In doing so this bill would close an unintended loophole in the existing law which, if uncorrected, could cause indigent veterans to lose benefits from VA assistance programs just because they were injured by exposure to Agent Orange. The VVA has been seriously concerned about the possibility that impoverished veterans could forfeit benefits from non-VA means tested assistance programs. Indeed, any program that utilizes a means test -- including Food Stamps, Child Nutrition and Support, SSI, AFDC, Medicaid, Earned Income Tax Credit, Guaranteed Student Loans, Subsidized Housing and Low Income Energy Assistance -- could be affected by payments from the Agent Orange Settlement Fund.

The VVA certainly supports this bill and urges the House Veterans Affairs Committee to move it forward, but it must be seen only as a first step in addressing this problem. Naturally, it would be preferable to have this particular measure amended to include exemption from other means tested assistance programs prior to passage and we will support such a move by the Congress.

VII. HR.3196/S.1692 AND HR.3486/S.1787

On September 17, 1987, upon introduction of S.1692, Senator Murkowski stated that "The evidence is not perfect; but it will never be perfect. Our understanding of cause and effect is still incomplete, but we will never have a complete understanding of disease and its causes.

"The essence of leadership is to know when the data is adequate to act.

"Leadership is a willingness to take action in the face of incomplete and imperfect data rather than accepting the paralysis inherent in a never ending wait for perfect understanding.

"The search for answers must continue; however, the constant desire for just one more study should not be an excuse for inaction."

These sentiments couldn't be more eloquently stated as a summation of the VVA's position even if we had written them ourselves. While the legislation introduced upon making these statements falls short, we have noted in Senator Murkowski's further remarks on September 17 that the measure introduced was requested by the DAV. It is our sincere hope that much stronger legislation, consistent with Senator Murkowski's definition of leadership, will be supported this year. Identical legislation, HR.3196, was introduced by Chairman Montgomery, also at the request of the DAV, on August 6, 1987.

In essence, HR.3196 provides a rebuttable presumption of service connection for one disorder, non-Hodgkins lymphoma. The justification given for selecting this particular disease as presumptively compensable is one with which we agree. The VA's own longitudinal mortality study, released last fall only after having been reported in the New York Times, showed that Marines who served in I Corps had a 110 percent greater liklihood of becoming afflicted with non-Hodgkins lymphoma than those having served outside of Vietnam. This finding is consistent with other studies that have shown an increased risk for NHL for persons exposed to the components of Agent Orange (i.e., the Kansas farmer study).

The presumption, however, is rebuttable. This means that in a future prospective claim for disability compensation under this legislation's provisions, the VA could deny service connection because of some other possible intercurrent reason for the appearance of non-Hodgkins lymphoma in the veteran claimant. We understand that this is consistent with other diseases presumed to be service connected in Title 38 which are also rebuttable. However, the VA's history on Agent Orange is replete with failure to resolve reasonable doubt as required in favor of the veteran on Agent Orange claims. As we have already pointed out in this statement, not one claim for compensation has ever been allowed for any veteran which acknowledged dioxin as the cause of disability. Of all Agent Orange claims up through to April 1, 1985, for example, 82.2 percent were denied. Those that were allowed, the remaining 17.8 percent, were granted for reasons other than Agent Orange exposure.

Our support for a non-rebuttable presumption is especially relevant with regard to our support of HR.3486. That legislation, which is preferred over HR.3196, allows a non-rebuttable presumption not only for non-Hodgkins lymphoma, but also for lung cancer manifesting itself within 25 years of departure from Vietnam. The presumption for lung cancer in HR.3486, like that of non-Hodgkins lymphoma in HR.3196, is based on the VA's longitudinal mortality study released last fall. Marines having served in I Corps had a 58 percent greater likelihood than individuals serving outside of Vietnam of becoming afflicted with lung cancer. Given the VA's history on this issue, as described above, we have to believe the VA would use a rebuttable presumption to rule out compensation for any veteran who ever smoked tobacco products, regardless of how infrequent or how long ago.

The minutes of the October 15, 1987 meeting of the VA's Advisory Committee on Environmental Hazards provide a rather telling justification for a presumption of service connection for lung cancer. During a portion of that meeting the VA's mortality study was being discussed and the subject of smoking as an intercurrent cause of higher rates of lung cancer in Marines having served in I Corps came up. One of the scientists deeply involved with the study, Dr. Kang, was asked about this finding. In providing an explanation the minutes recorded that, [H]e also agreed that smoking history would have been very valuable to include but that this type of study which relied on existing records, military records and death certificates would not include information on smoking patterns. He stated that they did attempt to look at other causes of death which might be associated with smoking (emphysema, bronchitis and other cancers associated with smoking) to determine whether they also were elevated and found ... no significant differences between veteran and non veteran Marines. In response to a question by Dr. Colton about any information that might exist about differences in exposure opportunities, Dr. Kang noted that 99% of the Marines stayed in I Corps whereas the Army was spread out through all four tactical zones of Vietnam." (emphasis added)

The reason that a 25 year delimiting period was selected in the legislation is that even a heavy smoker would be unlikely to get lung cancer within 25 years of departure from Vietnam, unless there were some other cause such as exposure to toxic herbicides. The average age of the typical service person in Vietnam was about 20 years of age. In order to be eligible for compensation under this provision of the bill, the average claimant would have to contract lung cancer by the age of 45, a most unlikely prospect unless he or she were exposed to dioxin.

Another aspect of the legislation would require the VA to contract with an unbiased non-govermental scientific entity for the purpose of determining, on the basis of a comprehensive review of all relevant and ongoing studies, which diseases are likely to result from the presumed immuno-suppressive effects of dioxin exposure. At the end of each year the review is undertaken, a list of these diseases would be provided to the VA. The VA would then be required to compensate veterans for these diseases on a non-rebuttable presumptive basis unless the Congress passed and the President enacted legislation to the contrary within 90 days of the VA's receipt of the disease list.

The VVA believes there is good reason to proceed with compensation for immunosuppressive effects of dioxin exposure because solid evidence derived from studies conducted in animals and human tissues exist to support both a review and compensation. Although there are many species specific toxic effects resulting from dioxin exposure, including chloracne, immunosuppression is one of the most consistent findings in all mammalian species thus far examined. The data from experimental animals further indicate that the immune system is one of the most sensitive organ systems to dioxin exposure; in many cases significant alterations in immune function parameters have been observed without any other physical alterations being apparent. In addition to being more susceptible to viral and bacterial infections, the ability of dioxin-exposed experimental animals to combat the maglignant growth of tumor cells is compromised. Furthermore, limited studies that have been conducted on certain human cells of the immune system indicate the same degree of sensitivity to dioxin as the same cell type from experimental animals. Given all of these findings it is logical to deduce that immunosuppression in humans may occur at some level of dioxin exposure.

A third aspect of the legislation would require the VA to evaluate the data already at its disposal to determine whether any disease patterns can be discerned on the basis of the thousands of veterans treated by the VA under the authority granted by P.L. 97-72. It is surprising to us that this has never been done.

Mr. Chairman, rather then expecting the Committee to rely on our judgement alone in the matter of immunosuppression, we have asked University of Rochester Associate Professor of Toxicology Thomas A. Gasiewicz, Ph.D. to supplement our presentation. Professor Gasiewicz' primary professional interest is in the biochemical and molecular mechanisms of toxicity. The major focus of his research since 1972 has been on the toxicity of dioxin. Professor Gasiewicz also served as a member of the peer review group chosen to review the Environmental Protection Agency's (EPA) Assessment Document for Polychlorinated Dibenyo - P - Dioxins. This is the EPA document that was produced to determine the health risk to humans, the process of which was described in section III of this statement. Addended to this statement are Professor Gasiewicz' views on the immunosuppressive affects of dioxin.

STATEMENT OF

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before the
SENATE VETERANS AFFAIRS COMMITTEE
on
AGENT ORANGE

May 12, 1988

Mr. Chairman and members of the Committee, my name is Thomas A. Gasiewicz. I received my Ph.D. in Toxicology in 1977 from the University of Rochester where now I am Associate Professor of Toxicology in the Department of Biophysics. In addition to spending the past 11 years in the research of various aspects of the mechanism of toxicity of the dioxins, which resulted in over 40 publications on this subject, I have given numerous lectures on this topic, and have served on governmental and non-governmental committees that have reviewed the toxicity of these compounds and their relative risk to human health (see submitted *curriculum vitae*).

Before continuing with the subject of the dioxins, it is pertinent for me to indicate that although I have been requested by the Vietnam Veterans of America, Inc. (VVA) to testify before this committee and will receive reimbursement for travel expenses, I have not received nor will accept additional compensation. My main purpose in being here today is to provide the VVA and this Committee with appropriate scientific information regarding the health effects of dioxin so that an informed decision can be made regarding the possible compensation of veterans exposed to Agent Orange and related herbicides used in Vietnam.

One of the goals of toxicologists working in this area is to characterize the human health risk of exposure to dioxins, and one of the means of approaching this is to identify the health effects elicited and determine the quantitative relationship between the specific exposure and the incidence or severity of the effect. Ideally, information from exposed human populations should be used. In the case of the dioxins, it is clear that some toxic effects such as chloracne have been observed in humans. However,it must be recognized that chloracne may not be, and is unlikely to be the most sensitive indicator of human exposure, but is the one that is most distinct and easily observed. Thus, while effects on more subtle and/or longer term responses such as cancer development and alterations of immune function have been suggested, these have not been **conclusively** demonstrated to occur in humans, and given the limitations of the data d these are unlikely to be conclusively demonstrated in the near future whether or not such effects really exist. Although there are many statistical reasons for this, including the small numbers of individuals in most exposed populations, probably the most important limitations are the lack of data on the amount of exposure and the inability of most studies to measure more sensitive indicators of toxic effects. Therefore, most, if not all, previous studies of humans exposed to dioxins are of limited use for determining quantitative exposure-response relationships and thus notably do not rule out the possibility of adverse effects in individuals of these exposed populations. In recent years the methodology has been developed for the sensitive and accurate measurement of dioxin in human tissues, and future studies of exposed populations may be able to confidently derive a relationship, positive or negative, between some exposure level and a certain toxic effect. To date, I am aware of only two studies to estimate human exposure levels to dioxin or a "dioxin-like" compound (2,3,4,7,8-pentachlorodibenzofuran) and to compare these levels with a toxic effect observed (chloracne). In one case, examination of contaminated food oil consumption data in a Japanese incident and blood values in a Taiwanese poisoning lead to an estimate of between 1.7 and 4.2 micrograms of 2,3,4,7,8-pentachlorodibenzofuran per kilogram body weight that could cause chloracne in a sensitive individual(or an approximate equivalent of 0.85 to 2.1 micrograms of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin)/ kilogram) (1). As you will see later in this discussion, these numbers are within the range of doses known to cause chloracne in experimental animals.

Due to the lack of appropriate human data, it is scientifically sound and appropriate that any human health risk assessment of dioxins consider the wealth of information available from animal studies. The use of this information has been the primary basis of risk assessments made on dioxin by state and federal agencies world wide. Although clearly these data are not perfect and a human differs biologically in many ways from experimental animals, these are the only data available for use and are likely to be so for many years to come. From all of these data come some consistent findings that are important for the commitee to consider. These are detailed below. It is first important to note that since these findings are consistent in all experimental mammalian systems yet examined, it is reasonable to deduce that at some exposure level, similar toxic effects are likely to be seen in humans.

1. Although quantitative differences in species sensitivity do exist, dioxin is extremely toxic to all mammalian species yet examined. Notably the approximate body burden shown to cause chloracne in animals ranges from approximately 0.03 micrograms dioxin (TCDD)/kilogram for the rabbit (2) to 9 micrograms/kilogram for monkeys (3). THe body burden levels of dioxin shown to cause chloracne in experimental animals are within the same range of that estimated to cause chloracne in individuals in the Japanese and Taiwanese incidents (to chlorinated dibenzofurans) (1) and German factory workers (to TCDD) (4).
2. Among the consistent effects seen in all mammalian species yet examined include body weight loss and effects on the immune system, including immunosuppression. As little as .002 to 0.1 microgram dioxin/kilogram has been shown to cause significant immune alterations in animals (5). These data indicate that the immune system is one of the most sensitive organ systems to dioxin exposure; in many cases significant alterations have been observed at levels not causing any apparent physical alteration. In addition, dioxin-treated animals have been shown to be more susceptible to viral and bacterial infections, and the ability to combat the malignant growth of tumor cells is compromised. Furthermore, more recent investigations have demonstrated the same degree of sensitivity of certain human cells of the immune system to dioxin exposure as compared to the same cell type from experimental animals (6).
3. Dioxin has been shown to be carcinogenic in all lifetime animal feeding studies yet

performed.

4. The toxic effects of dioxin are mediated through its ability to bind to a specific cellular protein (termed the Ah receptor) and to alter the manner in which DNA is expressed in cells. This receptor protein has been found in a number of human tissues, and experiments using human cells in culture (7) indicate the same degree of sensitivity as animal cells in regard to the ability of dioxin to modulate gene expression.

Again, given these consistent findings in all experimental animals yet examined and the similarity of the sensitivity and mechanism in the limitied number of human tissue studies, it is logical to conclude that similar effects may occur in humans. However, as noted above, for a variety of reasons, the past studies of exposed humans are of limited use. In addition, animal studies have noted that genetic differences may influence the degree of sensitivity towards dioxin. If this same parameter influences human susceptibility, it would be even more difficult for epidemiological studies to discern a relationship between exposure and any particular adverse effect given the vastly diverse genetic nature of a given human population. This would especially be true at exposure levels which may cause subtle, yet significant, toxic effects.

Finally, recent data have been put forth which indicate that some Vietnam veterans who were heavily exposed to Agent Orange have a body burden of dioxin which may be as high as 10-fold greater than "background" levels in a control population (8). The estimated level of this body burden in these individuals (approximately 0.5 μg/kg) (9) is at a level known to cause a number of non-lethal effects such as liver and reproductive alterations and immunosuppression in experimental animals.

In summary, in light of the limited usefulness of studies on exposed human populations, it is scientifically sound and appropriate for any committee reviewing the potential human health risks of the dioxins to consider not only the wealth of available information on experimental animals, but also the data from limited studies on human tissues. The consistent aspects of the experimental animal studies, the species homology of the mechanisms at the molecular level, and the similar sensitivities of human and experimental animal tissues all indicate a toxic significance of these compounds for humans. Furthermore, data suggesting an exposure of some Vietnam veterans to levels of dioxin known to consistently cause adverse health effects in experimental animals are of some concern.

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   Hong, R., Taylor, K., and Abonour, R. (1987). Immune abnormalities associated with chronic TCDD exposure in rhesus. Abstract of a paper presented at the 7th International Symposium on Chlorinated Dioxins and Related Compounds. Las Vegas, NV. October 4-9, 1987.
   Body burdens were estimated by T.A.G. as described in reference 2 above. A value for an estimated elimination half-time of 11 days was used for mice according to Gasiewicz *et al.*, 1983 (Gasiewicz, T.A., Geiger, L.E., Rucci, G., and Neal, R.A. (1983) Distribution, excretion, and metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin in C57BL/6J, DBA/2J, and B6D2F1/J mice. Drug Metab. Disp., 11, 397-403.). A value for an estimated elimination half-time of 365 days was used for monkeys according to McNulty *et al.*, 1982 (McNulty, W.P., Nielsen-Smith, K.A., Lay, J.O., Lippstreu, D.L., Kangas, N.L., Lyon, P.A., and Gross, M.L. (1982). Persistence of TCDD in monkey adipose tissue. Food Cosmet. Toxicol., 20, 985-987.).

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EDUCATION

INSTITUTION AND LOCATION	DEGREE	FIELD	YEAR
Canisius College, Buffalo, New York	B.S.	Chemistry	1972
The University of Rochester, Rochester, New York	Ph.D.	Toxicology	1977

PROFESSIONAL TRAINING AND EXPERIENCE

1972-77 Ph.D. Graduate Student, Department of Pharmacology and Toxicology, The University of Rochester, School of Medicine, Rochester, New York
1977-80 National Institutes of Health, Postdoctoral Fellow, Center in Toxicology, Department of Biochemistry, Vanderbilt University, Nashville, Tennessee
1980-86 Assistant Professor, Division of Toxicology, Department of Radiation Biology and Biophysics, The University of Rochester, School of Medicine, Rochester, New York
1986- Associate Professor, Environmental Health Sciences Center, Department of Biophysics, The University of Rochester, School of Medicine, Rochester, New York

HONORS AND AWARDS

1977-80 National Institutes of Health Postdoctoral Fellowship Award
1987-90 International Life Sciences Institute Research Foundation Award

MAJOR RESEARCH INTERESTS

Biochemical and molecular mechanisms of toxicity. Ligand-receptor interactions and the subsequent modulaton of gene expression by the halogenated aromatic hydrocarbons.

MEMBERSHIP IN PROFESSIONAL SOCIETIES

American Association for the Advancement of Science	1975-present
The New York Academy of Sciences	1979-present
Society of Toxicology	1982-present

EDUCATIONAL CONTRIBUTIONS

Graduate Students:

Major Advisor: Janet E. Kester, Ph.D., 1987, "Physicochemical Characterization of Rat Hepatic Ah Receptor and its Interaction with 2,3,7,8-Tetrachlorodibenzo-p-dioxin.

Mark E. Hahn, Ph.D., 1987, "Studies on the Role of the Ah Receptor in Hexachlorobenzene-induced Porphyria". First place graduate student award for meritorious research, Mechanisms Section, Society of Toxicology, 1987. Department of Biophysics Harold C. Hodge Scholarship Award, 1987.

Jay Fine, Ph.D., 1988 (tentative), "Characterization of the Mechanism of Altered Thymocyte Differentiation by 2,3,7,8-Tetrachlorodibenzo-p-dioxin".

Thesis Committee: Ph.D., 7 total; M.S., 3 total.

Postdoctoral Fellows: Joseph A. Sweatlock, 1982-85, NIH Postdoctoral Fellow.

Ellen C. Henry, 1984-88.

Courses:

a. Toxicology Core Course (TOX 521), 1980-present, 2-4 contact hours/year.
b. In Vitro Toxicology (TOX 593), 1984, 1 contact hour.
c. Biochemical Toxicology (ENV 463), 1984, 1 contact hour.
d. Seminar in Toxicology (TOX 558), 1984, 1985, 15 contact hours/year.
e. Special Topics in Immunotoxicology (ENV 492), 1984, 1986, 24 contact hours/year.

ADMINISTRATIVE ASSIGNMENTS

Toxicology Curriculum Committee, 1983-85.

PRESENTATIONS AT MAJOR NATIONAL PROFESSIONAL MEETINGS

Society of Toxicology, Atlanta, Georgia, 1976.
American Society for Pharmacology and Experimental Therapeutics, New Orleans, Louisiana, 1976.
Federation of American Societies for Experimental Biology, Chigago, Illinois, 1977.
Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, 1978.
Federation of American Societies for Experimental Biology, Dallas, Texas, 1979.
American Society for Pharmacology and Experimental Therapeutics, Portland, Oregon, 1979.
Federation of American Societies for Experimental Biology, Aneheim, California, 1980.
Society of Toxicology, Boston, Massachusetts, 1982.
Joint American Society of Pharmacology and Experimental Therapeutics/Society of Toxicology, Louisville, Kentucky, 1982.
Federation of American Societies for Experimental Biology, St. Louis, Missouri, 1984
Society of Toxicology, San Diego, California, 1985.
American Society for Pharmacology and Experimental Therapeutics, Boston, Massachusetts, 1985.
Society of Toxicology, New Orleans, Louisiana, 1986.
American Chemical Society, New York, New York, 1986.
American Association for the Advancement of Science, Philadelphia, Pennsylvania, 1986.

Joint American Society of Biological Chemists/American Chemical Society, Washington, D.C., 1986.
Joint American Society for Pharmacology and Experimental Therapeutics/Society of Toxicology, Baltimore, Maryland, 1986.
Society of Toxicology, Washington, D.C., 1986.
Society of Toxicology, Washington, D.C., 1987.

PARTICIPATION IN INVITED NATIONAL AND INTERNATIONAL MEETINGS, SYMPOSIUMS, SEMINARS

13th Annual Conference on Environmental Toxicology, Dayton, Ohio, August, 1983.
Biological Mechanisms of Dioxin Action, Cold Spring Harbor Symposium, Cold Spring Harbor, New York, April, 1984.
Symposium on Halogenated Dioxins and Dibenzofurans, Federation of American Societies for Experimental Biology, St. Louis, April, 1984.
Seminar Series on the "Ah Receptor", National Institute of Environmental Health Sciences, Research Triangle Park, November, 1984.
4th International Symposium on Chlorinated Dioxins and Related Compounds, Ottawa, Canada, 1984.
Gordon Research Conference, Mechanisms of Toxicity, Meridan, New Hampshire, August, 1985.
5th International Symposium on Chlorinated Dioxins and Related Compounds, Bayreuth, Germany, 1985.
Symposium on Receptor-Mediated Events in Toxicology, Federation of American Societies for Experimental Biology, St. Louis, April, 1986.
New York Academy of Sciences, Symposium on Chemical-Induced Porphyrinopathies, New York, November, 1986.
Chemical Industry Institute of Toxicology, "Biochemical Properties of the Ah Receptor and its Role in Gene Regulation and/or Toxicology of TCDD", invited seminar, Research Triangle Park, December, 1986.
Dioxin and Resource Recovery Symposium, New York, February, 1987.
Toxicology Forum Symposium, "Comparison of Genetic Versus Receptor Mediated Mechanisms in Carcinogenesis, Aspen, 1987.
International Life Sciences Institute Directors Meeting, "The Ah receptor: Its role in the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin", Atlanta, March 19, 1988.

OTHER PROFESSIONAL ACTIVITIES

Ad Hoc Reviewer, Veterans Administration Research Proposals, 1982, 1984, 1985.
Ad Hoc Review Committee, National Toxicology Program, National Institutes of Environmental Health Sciences, Research Triangle Park, August, 1984.
Peer Review Committee, Health Assessment Document on Polychlorinated Dibenzofurans, United States Environmental Protection Agency, Cincinnati, May, 1986; March, 1987.
Scientific Advisory Subcommittee, Dioxin Toxic Equivalency, United States Environmental Protection Agency, Washington, D.C., 1986.
Ad Hoc Reviewer, Promotions Committee, National Institutes of Environmental Health Sciences, November, 1986.
Expert Witness, Proposed Resource Recovery Facility, East Stroudsburg Zoning Hearing Board, Ease Stroudsburg, PA, September, 1987.
Scientific Advisory Board, Department of Environmental Protection, State of New Jersey, 1987-88.
Ad Hoc Panel on Health Aspects of Exposure to Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans, Universities Associated for Research and Education in Pathology (UAREP), FASEB, Washington, D.C., 1988.
Ad Hoc Reviewer, Research Proposals, Environmental Protection Agency, 1988.

Peer Reviewer for the following Scientific Journals: Archives of Toxicology, Chemical-Biological Interactions, Molecular Pharmacology, Journal of Pharmacology and Experimental Therapeutics, Toxicology and Applied Pharmacology, Journal of Toxicology and Environmental Health, Science, Life Sciences, Biochemical Toxicology, Pharmacological Reviews, Endocrinology, Journal of Biological Chemistry.

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RESEARCH GRANTS OBTAINED

Studies on the biochemical mechanism(s) of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) toxicity.
Agency: NIH (Postdoctoral Fellowship)
Period: 04/04/77-03/30/80

Molecular mechanisms of enzyme induction by the chlorinated-p-dioxins.
Agency: Pharmaceutical Manufacturers Association Foundation
Period: 01/01/81-12/31/82
Amount: $12,000
Role: Principal investigator

[illegible]
WASHINGTON D C 20201

APR 1 1983

MEMORANDUM FOR: Members, Domestic Policy Council
Agent Orange Working Group (DPC/AOWG)

FROM : Don M. Newman
Chairman, Domestic Policy Council
Agent Orange Working Group

SUBJECT : Clearance of all studies and press releases by the Domestic Policy Council Agent Orange Working Group

The Domestic Policy Council Agent Orange Working Group (DPC/AOWG) was created by President Reagan with the express mission of overseeing and coordinating Federal Government research activities relating to Agent Orange exposure and its possible health effects. The AOWG was given the responsibility for reporting to the public the results and implications of all research in the Agent Orange area.

The release of any report, without the review mandated by the Agent Orange Working Group procedures, could constitute a serious breach and may undercut our credibility. Any premature release could cause embarrassment to the government.

Research findings and conclusions must be submitted to the AOWG 48 hours prior to release for review, comment and clearance before going to Congress or the public. At a minimum, sufficient time must be allowed to prepare the Domestic Policy Council and the President for anything of significance.

Because of the emotional and sensitive nature of Agent Orange research, it is essential that each principal insist that this procedure be observed with the utmost care.

Your cooperation is appreciated.

Testimony of

David F. Carter, Chairman
Michael N. Sovick, Research Director

THE OKLAHOMA AGENT ORANGE FOUNDATION

Member of the National Association
of State Agent Orange Programs

before the

UNITED STATES HOUSE
COMMITTEE ON VETERANS' AFFAIRS

The Honorable G.V. (Sonny) Montgomery, Chairman

Wednesday, June 8, 1988

MEMBER OF THE NATIONAL ASSOCIATION OF STATE AGENT ORANGE PROGRAMS

THE OKLAHOMA AGENT ORANGE FOUNDATION
P.O. Box 849
Lexington, OK 73051
June 8, 1988

VIETNAM VETERANS DESERVE COMPENSATION, NOT MORE STUDIES

The Second Body Count of Dead Vietnam Veterans

Enclosed within this testimony are the summarized results from all of the Mortality and Morbidity studies that have been done on Vietnam Veterans. This compilation of results represents a data base of 765,664 men, nearly twenty-five percent (25%) of the total, with in-country service. Of these men, 39,989 have died since returning home. Thousands have died from latent diseases and disorders associated with exposure to toxic chemicals, including Agent Orange, in Vietnam.

Most of these studies have been completed since 1982, when the Reagan administration signaled a change in its cancer regulations, by stating it would "rely less on laboratory tests on animals and WAIT INSTEAD FOR EPIDEMIOLOGICAL STUDIES OF SICKNESS AND DEATH IN HUMAN POPULATIONS". Also in 1982 the Reagan administration REVISED the Veterans Administration (VA) literature, made available during the Carter administration to Vietnam Veterans inquiring about the human health effects of Agent Orange, by REMOVING ALL REFERENCES TO CANCER!

IS IT POSSIBLE THAT THOUSANDS OF VIETNAM VETERANS MAY HAVE DIED NEEDLESSLY BECAUSE THEY DID NOT RECEIVE THE NECESSARY INFORMATION ABOUT EARLY DETECTION FOR CANCER AND OTHER LIFE THREATENING DISORDERS?

Unfortunately, these revised cancer regulations may also have resulted in thousands of needless civilian deaths. For this reason, we have included summaries of studies done on civilians who were exposed to Agent Orange and its dioxin contaminant during the manufacturing process. (Other civilian health warnings were removed in 1982 by the EPA after the DOW Chemical Company was allowed to edit EPA documents.) After comparing these civilian studies with the studies done on Vietnam Veterans, we found that those civilians exposed to the same toxic chemicals as the Veterans have experienced similar excesses of death, birth defects, and illness of the same types of diseases and disorders.

VIETNAM VETERANS WERE EXPOSED TO HIGHLY CONTAMINATED TOXIC CHEMICALS, PERHAPS AS MUCH AS 47,000 TIMES AS TOXIC AS THE "CIVILIAN" VERSIONS. THUS, VIETNAM VETERANS MAY BE A "BAROMETER" FOR THE POPULATION AS A WHOLE, MUCH LIKE THE CANARIES THAT MINERS USED TO USE TO GIVE THEM AN EARLY WARNING ABOUT TOXIC GAS. PLEASE REVIEW THE SUMMARIES ABOUT THE CANARIES, VIETNAM VETERANS.

MEMBER OF THE NATIONAL ASSOCIATION OF STATE AGENT ORANGE PROGRAMS

THE OKLAHOMA AGENT ORANGE FOUNDATION
P.O. Box 849
Lexington, OK 73051
June 8, 1988

VIETNAM VETERANS DESERVE COMPENSATION, NOT MORE STUDIES

THE LATENT DISEASES AND DISORDERS OF THE LYMPHORETICULAR SYSTEM FOUND IN EXCESS: A REVIEW OF ALL OF THE MORTALITY AND MORBIDITY STUDIES OF VIETNAM VETERANS EXPOSED TO THE PHENOXY ACID HERBICIDES (AGENT ORANGE) AND DIOXIN (TCDD)

A. WHEN THE HUMAN BODY TRIES TO ELIMINATE TOXIC CHEMICALS, IMMUNE CELLS WITHIN THE LYMPHORETICULAR SYSTEM ARE INVOLVED IN THE DETOXIFICATION (OR ATTEMPTED DETOXIFICATION) & ELIMINATION PROCESS. THUS, THIS SYSTEM IS A POTENTIAL SITE OF DAMAGE AND SUBSEQUENTLY MAY BE THE SITE OF VARIOUS DISEASES AND DISORDERS. THE FOLLOWING LIST IS THE EVIDENCE OF EXCESS MORTALITY & MORBIDITY FROM DISEASES OF THE LYMPHORETICULAR SYSTEM IN VIETNAM VETS. (Numbered references, see page 6; abbreviation codes, see page 7)

THE LYMPHORETICULAR SYSTEM INCLUDES THE FOLLOWING:

1. LYMPHATIC - lymph nodes, lymph vessels, etc.
2. VASCULAR - heart, all blood vessels
3. RESPIRATORY -- nasal cavities, pharynx, mouth, larynx, bronchi, lungs, etc.
4. GASTROINTESTINAL - stomach, both intestines
5. GENITOURINARY - kidney, bladder, genitals, etc.

THE FOLLOWING IS THE EVIDENCE OF EXCESS LYMPHORETICULAR DEATH AND DISEASE EXPERIENCED BY VIETNAM VETERANS:

1. LYMPHATIC: CANCER - non-Hodgkin's lymphoma (NHL)

a.	VV	1983 VA Agent Orange Registry [25]	SSX
b.	VV	1985 NY Mortality Study [12]	MORX
c.	VV	1986 W. VA Mortality Study [10]	SSX
d.	VV	1987 CDC VES - Postservice Mortality[7]	XRR
e.	VV	1987 Ranch Hand II - Followup [5]	X
f.	VV	1987 VA Mortality Study [27]	SSX

2. VASCULAR: DISEASE - heart, blood vessels

    a. VV 1983 Mass. Mortality Study [13] SSX
    (cerebrovascular disease)

    b. VV 1984 Ranch Hand II - Baseline [17] SSX
    (abnormal peripheral pulses)

    c. VV 1985 NY Mortality Study [12] SSX
    (stoke & cardiovascular disease)

    d. VV 1987 CDC VES - Postservice Mortality[7] SSX
    (heart & cerebrovascular disease)

    e. VV 1987 Ranch Hand II - Followup [5] SSX
    (cardiovascular disease)

    f. VV 1988 Ranch Hand II - Interim Report [3] SSX
    (cardiovascular disease)

    g. VV 1988 CDC VES Physical Health [1] SSX
    (hypertension)

3. RESPIRATORY -- nasal cavities, pharynx, mouth, larynx, bronchi, lungs

a. CANCER

    (1). VV 1983 VA Agent Orange Registry [25] SSX
    (pharynx and buccal cavities)

    (2). VV 1984 Ranch Hand II - Baseline [17]
    (lip, oral cavity [buccal]) SSX
    (pharynx, and respiratory) X

    (3). VV 1985 NY Mortality Study [12] SSX
    (lung cancer)

    (4). VV 1986 W. VA Mortality Study [10] SSX
    (larynx and respiratory)

    (5). VV 1987 VA Mortality Study [27] SSX
    (lung cancer)

    (6). VV 1987 Ranch Hand II - Followup [5] X
    (oral cavity, pharynx, lung,
    and bronchus)

b. DISEASE

    (1). VV 1985 Wisconsin Mortality Study[11] SSX
    (pneumonia)

    (2). VV 1987 Ranch Hand II - Followup [5] SSX
    (TB, pleurisy, and rales)

c. FUNCTION

    (1). VV 1984 Ranch Hand II - Baseline [17] SSX
    (abnormal pulmonary function)

4. GASTROINTESTINAL: DIGESTIVE DISEASE - stomach, intestines

- a. OC 1983 Dow Occupational Study [26] SSX
  (digestive system morbidity)
- b. VV 1983 Correlates of A.O. Exposure [18] SSX
  (digestive problems - morbidity)
- c. VV 1984 Australian VV Mortality Study [14] XRR
- d. VV 1985 NY Mortality Study [12] MORX
- e. VV 1987 Ranch Hand II: Followup [5] X MORTALITY
- f. VV 1988 Disease Among Marines [2] SSX
  (digestive system morbidity)
- g. VV 1988 CDC VES Physical Health [1] SSX
  (gastrointestinal tract ailments)

5. GENITOURINARY - kidneys, bladder, genitals, etc.

a. CANCER

- (1). VV 1983 Mass. Mortality Study [13] SSX
  (kidney cancer)
- (2). VV 1984 Ranch Hand II - Baseline [17] X
  (kidney, bladder, & testicular)
- (3). VV 1985 NY Mortality Study [12] MORX
- (4). VV 1986 W. VA Mortality Study [10] SSX
  (testicular)
- (5). VV 1987 Ranch Hand II - Followup [5] X
  (kidney, bladder, & testicular)

b. DISEASE

- (1). VV 1985 Wisconsin Mortality Study[11] SSX
- (2). VV 1987 CDC VES - Mortality [6] SSX
- (3). VV 1988 Disease Among Marines [2] SSX

B. "Ranch Hand II: Baseline Morbidity Study Results" Lathrop et al., USAF, 24 Feb 1984, page XVII-13.

"There were 113 diseases reported by history in the Ranch Hands, but only 57 in the comparisons [mean number of conditions of 0.11 per person and 0.07 per person (p=0.02), respectively]."

A P-VALUE OF 0.02 INDICATES THAT A SIGNIFICANT AMOUNT OF EVIDENCE EXISTS THAT THE OBSERVED DIFFERENCE IN THE HEALTH STATUS BETWEEN THE TWO GROUPS IS REAL!

C. THE ADVERSE PSYCHOLOGICAL CONSEQUENCES OF DIOXIN: INCLUDING THE MORTALITY & MORBIDITY STUDIES DONE ON VIETNAM VETS.

Reference # year and type	Externally caused deaths	Mental disorders	Suicides
1) 1988 VV		SSX	
2) 1988 VV		SSX	
3) 1988 VV		SSX	
4) 1987 OC			SSX
5) 1987 VV		SSX	
6) 1987 VV	SSX		
7) 1987 VV	X	SSX	SSX
8) 1986 EN		SSX	
9) 1986 VV	SSX		SSX
10) 1986 VV	SSX		
11) 1985 VV	SSX	PMRX	SSX
12) 1985 VV	SSX	SSX	SSX
13) 1985 VV	SSX		SSX
14) 1984 VV	SSX		SSX
15) 1984 VV		SSX	
16) 1984 VV		SSX	
17) 1984 VV		SSX	
18) 1983 VV		SSX	
19) 1981 OC		X	
20) 1980 OC	X		X
21) 1977 OC	X		X
22) 1976 VV		SSX	
23) 1971 OC		SSX	
24) 1961 OC		X	

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ABBREVIATIONS

VV = Vietnam Veterans
OC = Occupational exposure
EN = Environmental exposure
XRR= Excess risk ratio
X = Excess
SSX = Statistically significant excess
MORX= Mortality odds ratio excess
PMRX= Proportionate mortality ratio excess

CANCERS FOUND IN EXCESS IN VIET VETS BY STATE STUDIES AND AGENT ORANGE PROGRAMS, THE USAF RANCH HAND II - BASELINE AND FOLLOWUP, THE CDC, AND THE VA. (Oklahoma Agent Orange Foundation-1988)

1983 VA A.O. Registry	LYMPHOMAS (NHL) PHARYNX or BUCCAL cavity
1983 Massachusetts	Soft-tissue sarcomas, Kidney
1984 Ranch Hand II Baseline	Skin (RH>C - more cancers) Systemic cancers (RH vs. Controls) Twice as many cancers of: Lip Oral cavity (BUCCAL) PHARYNX Testis (Testicular) Three times the cancers of: RESPIRATORY system and Intrathoracic (chest) Genitourinary system
1985 New York	LUNG Melanoma Leukemia NASAL LYMPHOMAS and Hodgkin's Genitourinary system Brain and CNS Soft-tissue sarcomas
1985 Wisconsin	Soft-tissue sarcomas, Pancreatic
1986 West Virginia	LYMPHOMAS RESPIRATORY LARYNX Hodgkin's disease Soft-tissue sarcomas Testicular
1987 CDC VES	LYMPHOSARCOMAS Leukemias Brain
1987 VA	LYMPHOMAS (NHL) LUNG All cancers combined
1987 Ranch Hand II Followup	Skin (RH>C - more neoplasms) Systemic Neoplasms (RH>C) Three times the cancers of: Oral Cavity (BUCCAL) PHARYNX Testis (Testicular) Two and a half times as many: Genitourinary system Twice as many cancers of the: BRONCHUS LUNG Soft-Tissue Sarcomas: Equal LYMPHOMA: Ranch Hand only

THIS CHART SHOWS THE CANCERS FOUND TO BE SIGNIFICANTLY EXCESS IN THOSE COUNTIES WHERE THE PHENOXY ACID HERBICIDES WERE, IN MANY CASES STILL ARE, MANUFACTURED. Abbreviations on the top line: Cer = Cervix, Kid = Kidney, Liv = Liver, Lun = Lung, Lym = Lymphoma, Rec = Rectum, Ski = Skin, Sof = Soft tissue, Sto = Stomach, ALL = all cancers combined, Nas = Nasopharyngeal, HD = Hodgkin's disease. (Elmo Zumzalt III, has HD as well as non-Hodgkin's lymphoma.) M = Male, F = Female, and B = both male and female combined. [Prepared from NCI data available since 1975.]

ID	St	County	Cer	Kid	Liv	Lun	Lym	Rec	Ski	Sof	Sto	ALL	Nas	HD
1														
2	AL	Tuscaloo								M				
3	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
4	AR	Pulaski	F			B								
5	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
6	CA	Alameda				B	B		B	M		B	B	F
7	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
8	FL	Orange				M			M				F	
9	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
10	IA	Page											F	
11	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
12	IL	Cook		B	B	B	B	B			B	B	B	
13		Du Page				M	B						B	
14		St. Clai	F			M		M				B	F	
15	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
16	KS	Sedgewic	F				M			M			M	
17		Wyandott	F			M			F			M	F	
18	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
19	MD	Hartford										F		
20	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
21	MI	Midland												
22	--	--------	---	---	---	---	---	---	---	---	---	---	---	--
23	MN	Ramsey		B	F		B	M		F	F	B		B
24	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
25	MO	Buchanan	F							F				
26		Greene					M							
27		Lawrence							F					
28		St. Loui		F		B				M				
29	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
30	NJ	Essex		M		B	M	B			B	B		B
31		Middlese		M		M		B	M		B	M	F	F
32		Passaic		B		B		B			B	B	B	F
33		Union		M		M	M	B			B	B		B
34	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
35	NY	Niagara				M		M		F		B		B
36	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
37	OH	Cuyahoga		B	B	B	B	B			B	B	F	B
38		Tuscaraw								F			F	
39	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
40	OR	Multnoma				M				B		B		B
41	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
42	PA	Montgome						M		M			M	B
43		Philadel		M	B	B		B		M	B	B	M	
44	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
45	TX	Jefferso			M	B						M		
46	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
47	WA	Pierce												M
48	--	--------	---	---	---	---	---	---	---	---	---	---	---	---
49	WV	Kanawha			M	M								

THIS CHART CONTAINS DATA FROM ALL KNOWN STUDIES OF HUMAN IMMUNE SYSTEM DYSFUNCTION RESULTING FROM EXPOSURE TO DIOXIN OR OTHER STRUCTURALLY SIMILAR HALOGENATED HYDROCARBONS. (For abbreviations see page 12.) NOTICE THAT THE CONSEQUENCES OF EXPOSURE: CANCER, INFECTIOUS DISEASE, AND OTHER DISEASES ARE ALL INCREASED, IN SIGNIFICANT EXCESS, IN THE FOLLOWING EXPOSED HUMAN POPULATIONS: YUSHO, MICHIGAN, SEVESO, STRUGEON, MO., AND RANCH HAND.

ID	Study	TTC	T4H	T8S	OTC	TBC	Com	PHA	PWM	DTH	Tet	C	I	O	T
1															
2	Coalite						D	D							C
3															
4	Yusho	D								D		I	I	I	C
5															
6	Michigan	D							D	D		I	I	I	C
7															
8	Seveso						I	I	I			I	I	I	A
9															
10	Taiwan	D	D				D			D				I	C
11															
12	Strugeon	D			D							I	I	I	A
13															
14	Stehr				D									I	C
15															
16	Falk				D								I	I	C
17															
18	Knutsen 84		D	D	D					D	D				C
19															
20	RanchHand8	D		D		D		D				I	I	I	C
21															
22	Texas A.O.		D	D	D			D				I		I	C
23															
24	JAMA MO		D		D				I	D			I	I	C
25															
26	Reims, Fr.		I	D											A
27															
28	Lovelace			D	I	I									C
29															
30	Knutsen 87	D	D		D					D					C
31															
32	RanchHand8	D		D					D			I	I	I	C
33															
34	CDC VES 88												I	I	C

ID 8	SEVESO	"A net increase was found for 1977 over the previous year, rising from a total of 483 to 1219." *** THIS REPRESENTS A 250% INCREASE IN INFECTIOUS DISEASE, AFTER DIOXIN EXPOSURE!
ID 20	RANCH HAND	"There were 113 diseases reported by history in the Ranch Handers but only 57 in the comparisons." *** A STATISTICALLY SIGNIFICANT INCREASE P=0.02.
ID 22	JAMA MO	Significant excess/"other miscellaneous diseases".

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EXPLANATION OF ABBREVIATIONS USED WITHIN IMMUNOSUPPRESSION CHART

Top line of chart:

Quantitative
TTC = Total T-cells
T4H = T4 helper cells
T8S = T8 cytotoxic/suppressor cells
OTC = T4/T8 ratio (other t-cells)
TBC = Total B-cells

Functional
Com = Complement or immunoglobin
PHA = Phytohemagglutinin
PWM = Pokeweed mitogen
DTH = Delayed type hypersensitivity
Tet = Tetanus toxiod

CONSEQUENCES
C = Cancer
I = Infectious disease
O = Other disease

T = Type of exposure
A = Acute
C = Chronic

Letters within the chart: I = Increase, D = Decrease

Q. THIS CHART IS A SUMMARY OF THE BIRTH DEFECTS DATA FROM STATE AGENT ORANGE PROGRAMS & MDL 84-6273.(Prepared by: OK.A.O.F.)

ID	State	Number of Claims	Birth Defects	Fetal Death	Other
2	CN	N = 1928 Claims	180 = 9.3%	106 = 5.5%	
4	MA	N = 1907 Births	662 = 34.7%		Special Ed 122 = 6.4%
6	OK	N = 1207 Claims		224 = 18.6%	
8	OR	N = 2078 Claims	562 = 27%	594 = 29%	Stillbirth 57 = 2.7%
10	TX	N = 346 Claims	80 = 23.1%	79 = 22.8%	
12	WA	N = 5244 Claims	1206 = 23%		
14	WVA	N = 354 Claims	73 = 21%		
16	MDL	N = 231,309	68,878 = 30%	38,667 =17%	

ID 2 Connecticut Agent Orange Commission, Connecticut Morbidity Study Results, March 1984. [see A.O. 1#10]

ID 4 Massachusetts Agent Orange Program, Health Survey of Massachusetts Vietnam Veterans, June 1986.

ID 6 Oklahoma Agent Orange Commission, Oklahoma Agent Orange Assistance Program Tally Sheet, July 25, 1986.

ID 8 Oregon: The Vietnam Veterans Benefits Act of 1983, Final Report, October 1986. [see A.O. Report 16#8]

ID 10 Texas Veterans Agent Orange Assistance Program, Data Sheet, March 31, 1983.

ID 12 Washington State Department of Veterans Affairs, Hotline Information, June 30, 1985.

ID 14 West Virginia Agent Orange Assistance Program, Veteran Summary Letters, May 31, 1986.

ID 16 Agent Orange Product Liability Litigation Data Base, MDL 84-6273, March 20, 1984.

Texas Veterans Agent Orange Assistance Program, Summary of the Univ. of Texas Agent Orange Birth Defects Study, 26 March 1984.

> **This study found a marginally statistically significant excess of children, with PATERNAL TCDD exposure, who have presented sporadic chromosomal abnormalities, a new auto-dominant mutation, or a birth defect of certain etiological classes; when compared to the frequency in the fathers of control children (with no exposure).**

THIS CHART IS A SUMMARY OF MOST OF THE HUMAN BIRTH DEFECT STUDIES ON THE HERBICIDES 2,4-D, 2,4,5-T, AND AGENT ORANGE, INCLUDING THE BIRTH DEFECTS FOUND IN SIGNIFICANT EXCESS IN THOSE U.S. COUNTIES WHERE THESE HERBICIDES WERE, OR STILL ARE, MANUFACTURED. (See page 16 for an explanation of the abbreviations.)

ID	St	County or Study	ALL	ASB	CAH	VAD	ASD	PDA	DWS	HMD	T	H	C	S
1														
2	IL	Cook 1/1			NWM				AW					
3		Du Page 1/1			NWM				AW					
4														
5	KS	Sedgewick/1,28,8						AW		M&F				
6		Wyandotte 1/7								NWM				
7														
8	MI	Midland 1970-75											+	+
9		Midland 1976-81										+		
10														
11	MO	St. Louis 1/1						NW						
12														
13	OH	Tuscarawas 1/12								M				
14														
15	PA	Montgomery 1/4								NW				
16		Philadelphia 1/4								NW				
17														
18	WA	Pierce 1/1				M								
19														
20	WV	Kanawha /16,8,28		F	M					M				
21														
22		Arkansas CleftPL											+	
23														
24	P	Australian VV			+	+			+					
25														
26	P	CDC JAMA 1984		+									+	
27	P	CDC Monograph 84		+		+		+			+		+	+
28														
29		Chlorophenol6/29					+					+		
30		Multnomak 8-10	+											
31		Montgomery8-10	+											
32		Ramsey 8-10	+											
33		Sedgewick 8-10	+											
34														
35	P	Dow												
36														
37	P	NIOSH									+			
38														
39	P	NZ 2,4,5-T												
40														
41		NZ Herbicide Spr	+		+						+			+
42														
43	P	Ranch Hand 1984	+	+										
44														
45		Seveso (Bruzzi)			+				+					
46														
47	P	Vietnam (Can et	+										+	
48														
49	P	Vietnam (Lang et	+											
50														
51		Seveso (JAMA 88)												+
52														
53	P	CDC VES 1988	+											

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REFERENCES: BIRTH DEFECTS CHART

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EXPLANATION OF ABBREVIATIONS WITHIN BIRTH DEFECTS CHART

Top line of the chart:

ALL = All congenital anomalies
ASB = Anencephalus and spina bifida
CAH = Congenital anomalies of the heart
VSD = Ventricular septal defect
ASD = Atrial septal defect
PDA = Patent ductus arteriosus
DWN = Down's syndrome
HMD = Hyaline Membrane disease
T = Talipes (foot defects)
H = Hip defects
C = Cleft palate or lip
S = Hypospadias or epispadias (penis defects)

Within the chart:

NWM = Non-white male
AW = All whites
NW = Non-white
M = Male
F = Female
+ = Statistically significant defect

Between ID 2-20, e.g., 1/1, /1 = one of one statistically significant county out of all of the counties in the U.S.

e.g., 1/7 = one of seven statistically significant counties.

Between ID 24-53, P = Paternal exposure.

Between ID 30-33, 8-10 = counties with statistically significant excess of 8-10 birth defects.

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DISINFORMATION (MISINFORMATION) ABOUT TCDD LEVELS: A CDC "PERCEPTION GAP" BETWEEN THE BELIEFS OF THE CDC AND IT'S SCIENTISTS AND THE REALITIES OF WHAT HAPPENED TO MILITARY PERSONNEL IN SOUTH VIETNAM

Recently a published report from the Centers for Disease Control (CDC), found in both their Morbidity and Mortality Weekly Report (MMWR 36(28):471) and in the Journal of American Medical Association (JAMA 258:751), stated in part that median TCDD (tetrachlorodibenzo-p-dioxin) levels "were virtually the same" for Vietnam Veterans and non-Vietnam Veterans. A CDC editorial note within the report stated, "(t)he purpose of this study was to determine whether estimates of exposure based on military records or on interviews of U.S. Army veterans can identify those with heavy exposure to TCDD". The CDC continues, "(s)erum TCDD levels measured in 1987 were not associated with any of the indirect exposure scoring methods evaluated". Also, the CDC said, "(t)he distribution of TCDD levels reported here cannot be generalized with confidence to all U.S. Army Vietnam Veterans since the study did not use a random sample of all such veterans". In other words, this CDC study is NOT A VALID STUDY, because the cohorts were not randomly sampled and because these INVALID TCDD LEVELS were used to try to validate NON-EXISTENT military exposure records.

The CDC report claims it has deliberately over-sampled men with "higher exposure scores". However, within Table 1, on page 473 of the MMWR, we find that only 29% of the three Vietnam Veteran cohorts are in the "high exposure score" category. On the other hand, the "low exposure score" category contains 46% of the total study group. Clearly, these data in this table show that the men with "higher exposure scores" WERE NOT OVER-SAMPLED as the CDC claimed. Also, from Table 1, we find that the CDC's "high exposure group" had fewer men that were either draftees or had tactical MOS's (a combat military occupational specialty). In effect, this would have under-sampled exposure in the "high exposure" category because there are fewer combatants, a sub-group more prone to exposure. Table 1 shows that the non-Vietnam Veteran control group was 59% more likely to have civilian occupational exposure to herbicides than the Vietnam Veterans that were sampled. The bottom line here is that the CDC compared a deliberately under-sampled "high exposure group" within the larger "exposed" cohort with a deliberately higher exposed control group. Again, this clearly shows that THE CDC DID NOT OVER-SAMPLE EXPOSED VIETNAM VETERANS with "higher exposure scores" but rather THE CDC DELIBERATELY OVER-SAMPLED HIGH EXPOSURES IN THE CONTROL GROUP. THIS IS DISINFORMATION.

More about how the CDC compares "apples with oranges". The CDC reported in this study that the median serum TCDD levels between the two groups "were virtually the same" and that the highest level found in the exposed group was below "the upper limit for unexposed U.S. residents". The CDC is actually comparing MEDIAN SERUM (BLOOD) LEVELS with MEAN ADIPOSE (FAT) TISSUE LEVELS. This is just like trying to compare apples with oranges. They took this adipose tissue level from Table 2 (Comparison of the Adipose Tissue Concentrations of TCDD in Populations With No Known TCDD Exposure) from a journal article, "2,3,7,8-tetrachlorodibenzo-p-dioxin Levels in Adipose Tissue of Exposed and Control Persons in Missouri" (JAMA 256:2683), written by CDC scientists. By comparing MEDIAN with MEAN, and BLOOD with ADIPOSE TISSUE (FAT) the CDC has used DISINFORMATION, AGAIN.

Also, this same study (JAMA 256:2683, 1986) states that, "(p)rior to this report, the two highest levels of TCDD in adipose tissue were (1) 1840 ppt..." "...and (2) 130 ppt...". However, in Gross et al., "Tetrachlorodibenzo-p-dioxin Levels in Adipose Tissue of Vietnam Veterans" (Environ. Res. 33:261-268, 1984), both the abstract and the study clearly describe a sample, from a Vietnam Veteran exposed to Agent Orange as containing 173 ppt. Clearly, this amount, 173 ppt, should have been the second highest amount mentioned. THIS IS MORE CDC DISINFORMATION ABOUT DIOXIN LEVELS IN VIETNAM VETERANS.

In summary, the CDC authors of these two articles, the MMWR report and the Missouri study (JAMA 256:2683), use disinformation to misinform health care professionals, the media, the public, and Vietnam Veterans and their families about the truthful information concerning Agent Orange and dioxin exposure. Should those individuals responsible for this disinformation be held accountable for the illness and additional deaths due to lack of appropriate health care information?

BRIEF CRITIQUE OF THE CDC DIOXIN SERUM LEVEL STUDY

1. The CDC claims that men with "high exposure scores" were over-sampled; HOWEVER, THE CDC ACTUALLY OVER-SAMPLED HIGHLY EXPOSED CONTROLS (instead of highly exposed Vietnam Vets).

2. The CDC INCORRECTLY compares MEDIAN serum (blood) levels of dioxin with MEAN adipose (fat) tissue levels.

3. The CDC OMITS a previously reported HIGH LEVEL OF DIOXIN FOUND IN A VIETNAM VETERAN. (in another article)

4. THE BOTTOM LINE: The CDC states, "(t)he distribution of TCDD levels reported here cannot be generalized with confidence to all U.S. Army Vietnam Veterans since the study did not use a random sample of all such veterans."

5. O.T.A. reviewers: "For self-reported indirect exposure, CDC did find an association of dioxin levels with categories."

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DIFFERENCES BETWEEN THE "J.A.M.A." (Journal of the American Medical Association) AND THE CDC (Centers for Disease Control) MONOGRAPH VERSIONS OF THE CDC VIETNAM EXPERIENCE STUDY (VES).

	CDC JAMA VERSION		CDC MONOGRAPH VERSION
1.	Medical data used based on death certificates. [Less accurate]	1.	Medical data used based on review of medical records.[More accurate]
2.	"There was no particular type of neoplasm in excess in the Vietnam cohort."	2.	"Examination of specific types of cancer shows more deaths amoung Vietnam Veterans from brain cancers, leukemia, and non-Hodgkin's lymphomas, all in very small numbers."
3.	Risk ratio for neoplasms 0.82.	3.	Risk ratio for neoplasms 1.21. [Excess]
4.	Found excess post-service mortality similar to other men returning from combat areas after WWII and Korea.	4.	Did not explain that Vietnam veterans actually are experiencing similar post-service mortality as ex-POW's from WWII and Korea.
5.	Describe statistically significant excess deaths due to external causes.	5.	Statistical significance for external causes lost.
6.	Report a 0.95 risk ratio for mental disease.	6.	Report a 2.85 risk ratio for mental disease ($p<.06$). [Excess]
7.	No mention of autoimmune diseases.	7.	Autoimmune diseases, including lupus, were found.
8.	Released to the media for public consumption and published in JAMA.	8.	NO MEDIA RELEASE OF THE MORE ACCURATE DATA IN THE CDC MONGRAPH.

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DIFFERENCES BETWEEN THE "J.A.M.A." (Journal of the American Medical Association) AND THE CDC (Centers for Disease Control) VERSIONS OF THE CDC VIETNAM EXPERIENCE STUDY (VES), HEALTH STATUS OF VIETNAM VETERANS, II. PHYSICAL HEALTH.

CDC TESTIMONY BEFORE THE SENATE or JAMA EMBARGOED NEWS RELEASE and subsequent news reports based on these 2 items.	WHAT THE JAMA ARTICLE ACTUALLY SHOWS OR REPORTS (* - the Ranch Hand Studies found similar results)
1. "Physical and laboratory examinations shows few current differences between the two groups despite the many differences elicited by telephone interview." (CDC, James O. Mason, Senate testimony - 5/12/88) "On examination, we found no differences between cohorts in these health effects, such as skin conditions,... ...hepatic dysfunction,...". (JAMA news release - 5/12/88) "No difference in fertility between the two groups was found." (JAMA news release) "...the prevalence of reported medical problems among those examined was similar to the prevalence in the total telephone interview group." (JAMA article - 5/13/88)	1. MEDICAL EXAMINATION OF VIETNAM VETERANS ACTUALLY FOUND STATISTICALLY SIGNIFICANT EXCESSES OF: a. * Health status "fair/poor" b. Somatic symptoms c. * Hypertension d. CHLORACNE and other skin conditions e. * Other liver conditions f. Fertility difficulties g. Decreased concentration and proportion of normal sperm cells. h. High-freq. hearing loss i. * Increased fasting glucose j. * Higher mean thyroid stimulating hormone k. Stool occult blood l. Evidence of past hepatitis B infection
2. "Vietnam Veterans Health Held No Worse Than Others"- "The problems are termed psychological, not physical." (NY Times, 5/13/88)	2. THE MANY DOCUMENTED PHYSICAL HEALTH PROBLEMS OF VIET VETS WERE NOT MENTIONED IN: JAMA, SENATE TESTIMONY OR THE MEDIA.

THE UNDER SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JUN 9 1988

The Honorable G.V. (Sonny) Montgomery
Chairman
House Committee on Veterans' Affairs
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

As I promised in my letter to you of April 21, 1988 enclosed is the review you requested of the Interim Report by Dr. Richard A. Albanese entitled "United States Air Force Personnel and Exposure to Herbicide Orange" (USAFSAM-TR-88-3).

I requested the Science Panel of the Domestic Policy Council Agent Orange Working Group (DPC/AOWG) to conduct an indepth review of the study and I am appending both the summary report from Dr. Ronald Hart, who chairs the Science Panel and the individual comments of key members of the panel. There is unanimity of opinion as to the merits of this report and the findings which warrant follow up investigation or analysis are identified.

Please do not hesitate to contact me should you have further questions.

Sincerely,

Don Newman

Don M. Newman
Chairman,
Domestic Policy Council
Agent Orange Working Group

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Phone: (501) 541-4000
(FTS) 790-4611

National Center
For Toxicological Research
Jefferson AR 72079

MAY 23 1988

The Honorable Donald M. Newman
Chairman, Domestic Policy Council
Agent Orange Working Group
Department of Health and Human Services
200 Independence Avenue, S.W.
Room 614-G, HHH Building
Washington, D. C. 20201

Dear ~~Mr. Newman~~ Don:

In response to the Congressional request, the AOWG Science Panel members were asked to review the Interim Report by Dr. Richard A. Albanese entitled "United States Air Force Personnel and Exposure to Herbicide Orange" (USAFSAM-TR-88-3). I would like to submit to you the enclosed summary along with the individual reviews in response to this request.

I wish to thank the following individuals for taking time to review this report and submit written comments: Dr. Vernon N. Houk, CEHIC/CDC; Dr. Marilyn A. Fingerhut, NIOSH/CDC; Dr. Lawrence B. Hobson, VA; Drs. Terry L. Thomas and Han K. Kang, VA; Dr. Carl A. Keller, NIEHS; and Dr. John F. Young, NCTR. Reviews from the Air Force members of the AOWG Science Panel are obviously missing; this is by design due to the controversy surrounding this article. Ms. Hellen Gelband's OTA review was not included with this summary by choice since it was sent directly to Congress in response to their own Congressional request; however, there are no inconsistencies between the reviews. A copy of the OTA review is included for your perusal, but not for inclusion with the rest of the AOWG Science Panel reviews.

At the AOWG Science Panel meeting scheduled for June 1, 1988, this report will be open for discussion.

If more information is needed, please do not hesitate to ask.

Sincerely,

Ronald

Ronald W. Hart, Ph.D.
Chairman, AOWG Science Panel
Director, NCTR

Enclosures

Summary of AOWG Science Panel Reviews of "United States Air Force Personnel and Exposure to Herbicide Orange" by Richard A. Albanese, February, 1988. (USAFSAM-TR-88-3)

Reviews were submitted by Dr. Vernon N. Houk, CEHIC/CDC; Dr. Marilyn A. Fingerhut, NIOSH/CDC; Dr. Lawrence B. Hobson, VA; Drs. Terry L. Thomas and Han K. Kang, VA; Dr. Carl A. Keller, NIEHS; and Dr. John F. Young, NCTR. [The individual reviews are attached as part of this summary.]

This report is a reassessment of the Baseline Morbidity Study Results from the 1984 AFHS of Ranch Hand veterans. Several of the reviewers questioned why the data were being reassessed at this time, why this reassessment did not take into account the literature references since 1984, and especially why the October, 1987 AFHS, First Followup Examination Results report was ignored? It would appear that Dr. Albanese has only slightly modified the original 1984 document to make a case to implicate Agent Orange in some findings of rather questionable significance. Of the five "significant" clinical areas mentioned by Dr. Albanese as being in excess among the Ranch Hand group, one is still undergoing validation (patent-reported birth defects) and the other four are not supported by the October, 1987 AFHS followup report.

There was general criticism of this technical report in respect to its lack of detail on study methodology, statistical procedures, and definitions of terminology. There was also a lack of consistency in the statistical analysis and data presentation from one table to the next. (Table 12, p. 21, is clear and contains sufficient information; however, it is the only one with this format.)

There is general agreement that the results from this study can neither implicate nor exonerate Agent Orange as the causative agent. However, with the current (1988) state of knowledge and ability to quantitate the TCDD serum levels of these individuals, this continuing research effort of the AFHS has the potential to provide very useful information regarding health effects in Agent Orange "exposed" individuals.

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Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, DC 20510-8025

JOHN H. GIBBONS
DIRECTOR

May 6, 1988

The Honorable G.V. Montgomery
Chairman
Committee on Veterans' Affairs
U. S. House of Representatives
Washington, D.C. 20515

Dear Sonny:

Enclosed is the review that you and your colleagues requested in your letter of March 30, 1988, of the report entitled "United States Air Force Personnel and Exposure to Herbicide Orange" (referred to hereafter as the "Report"). The Report takes a second look at data presented by the Air Force in its 1984 report of the first morbidity results from the Air Force Health Study (AFHS).

According to OTA staff who reviewed the study, and contrary to Dr. Albanese's introduction, the Report does not diverge greatly from the original Air Force interpretation, and no new findings emerge from it. Dr. Albanese has not taken issue with the original analyses, except in the case of cancers. His analysis, however, in our opinion, is not more appropriate than the original one performed by the Air Force. While his approach is not wrong, it does not add information.

The main concern expressed by Albanese is that the 1984 findings not be taken as proof that Agent Orange is not affecting the health of the Ranch Hands. To support his concerns, he cites animal studies and other epidemiologic studies, and highlights selected AFHS findings in which significant differences between Ranch Hands and comparisons were found. Dr. Albanese also comments on the weakness of the Agent Orange exposure estimates used. The method Albanese used in putting together his observations does not represent a particular study design, in the usual sense of the phrase, and it is not subject to a formal independent quantitative analysis.

The major areas in which Albanese noted evidence which he judged to support an effect of Agent Orange are commented on in the enclosed Staff Paper, and corresponding information in those subject areas from the AFHS second examination (published in 1987) is added.

The Report by Dr. Albanese does not call into question any of the findings reported directly by the Air Force study team in their original reports. Albanese does draw attention to the fact that the study results cannot be taken to mean that Agent Orange is not harmful, or that the Ranch Hands are entirely free of any effects. The AFHS is limited by its size and by the relatively young age of the participants.

Other than continuing to study this group, as is planned, and to use new technology to determine dioxin body burdens, the reinterpretation does not suggest new directions for AFHS.

I hope this OTA review is helpful to you. If you have any questions, please do not hesitate to contact me, or Hellen Gelband in the OTA Health Program (8-6590), who was responsible for this review.

Sincerely,

Jack

John H. Gibbons

enclosure

OTA Review of:

"United States Air Force Personnel and Exposure to Herbicide Orange" Richard A. Albanese, M.D., February 1988 (USAFSAM-TR-88-3)

Staff Paper
Prepared by Hellen Gelband

Special Projects Office of the Health Program

Office of Technology Assessment
U.S. Congress

May 1988

The views expressed in this Staff Paper do not necessarily represent the views of the Technology Assessment Board or its individual members.

MAY 1988

OTA Review of:

"United States Air Force Personnel and Exposure to Herbicide Orange"
Richard A. Albanese, M.D., February 1988 (USAFSAM-TR-88-3)

This review was prepared in response to a March 30, 1988, letter from the Chairmen and Ranking Minority Members of the House and Senate Veterans' Affairs Committees, asking that OTA provide comments on the technical aspects of this report.

The reinterpretation of results of the first Air Force Health Study morbidity report (AFHS)[1], by Richard A. Albanese, M.D., does not diverge greatly from the original Air Force interpretation, and no new findings emerge from it. Albanese has not taken issue with the method of the analyses (except in the case of cancers, discussed below), nor with the analytic results. The main concern expressed by Albanese is that the 1984 findings not be taken as proof that Agent Orange has not affected or will not in the future affect the health of Ranch Hands. To support his concerns, he cites animal studies and other epidemiologic studies, and highlights selected AFHS findings in which significant differences between Ranch Hands and comparisons were found. Dr. Albanese also comments on the Agent Orange exposure estimates used. This reinterpretation does not have a particular study design, in the usual sense of the phrase, and it is not subject to a formal independent quantitative analysis.

The major areas in which Albanese noted evidence which he judged to support an effect of Agent Orange (in his summary table 19) are commented on below, and corresponding information in those subject areas from the second examination[2] is added. In general, from the first to the second morbidity reports, some shifts have occurred, with the Ranch Hands having slightly better test measurements than the comparisons in some cases, and slightly worse in others.

---

[1] Lathrop, George D., Wolfe, William H., Albanese, Richard A., and Moynahan, Patricia M., Air Force Health Study (Project Ranch Hand II): An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides, Baseline Morbidity Results, 24 February 1984.

Exposure Index

Albanese states a major concern about the exposure index used in the study, commenting that misclassification may obscure Agent Orange dose-related relationships. This has also been a concern of the Ranch Hand researchers. If the Air Force implements its proposal to measure blood dioxin levels in the study population, this issue should be greatly clarified, though undoubtedly a certain amount of misclassification will still remain. Until these measurements are made, there is no way to estimate the effect of misclassification.

Neoplasia

Albanese reinterprets the data on cancer, asserting that, for all malignant cancers combined, the rate in the Ranch Hand group is about twice as high as the original control group, and that the difference is statistically significant. The main Air Force 1984 analysis split cancers into those of the skin and all others, categorized as systemic. They reported a significant excess of skin cancers (the vast majority in both groups being generally curable nonmelanomas) in the Ranch Hand group, but no difference in systemic cancers. Albanese criticizes this separate analysis as being based on a decision made after the data had been examined, rather than on a plan stated in the study design.

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[2] Lathrop, George D., Wolfe, William H., and co-authors, Air Force Health Study: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides, First Followup Examination Results, October 1987.

MAY 1988

Nonmelanomas are the commonest malignancies in relatively healthy, middle-aged men, and the total number of cancer cases in this study is dominated by them. While it is not wrong to look at total cancers, it is of greater epidemiologic interest, where numbers of cases are sufficiently large, to identify more specific types of cancer in which the groups differ, rather than to claim an excess in a broader category. Albanese himself did not hypothesize that one would expect an overall increase. Because the numbers of each specific type of systemic cancer are small in both groups, it is not possible to analyze each one separately, though that is theoretically desirable. Lumping all cancers together does give greater overall power to detect an excess in total cancers, but it produces cruder information than do site-specific analyses. In this case, stating that there appears to be an excess of skin cancers (specifically, nonmelanomas) is more informative and uses the data better than does a claim of excess total cancer.

The numbers Albanese chose to include in his analysis of neoplasia may be influenced by a bias that, as far as can be detected, is not mentioned by Albanese or by the 1984 report. Albanese bases his analyses on data from Ranch Hands and original comparisons who were both interviewed and examined (1045 Ranch Handers and 773 original comparisons). The 1984 report gives both these figures and those for the group that completed the interview only. For cancers, he reports the following numbers of confirmed (by medical or pathological records) cases:

TABLE 1

Group	Skin Cancer No. (%)	Systemic Cancer No. (%)	Total
Ranch Hand	35 (3.3)	13 (1.2)	1,045
Comparison	10 (1.3)	8 (1.0)	773

The corresponding numbers from all interviewed Ranch Hands and original comparisons are the following:

TABLE 2

Group	Skin Cancer No. (%)	Systemic Cancer No. (%)	Total
Ranch Hand	35 (3.0)	14* (1.1)	1,174
Comparison	15 (1.6)	10 (1.0)	956

*one of these men died between interview and examination

A comparison of the figures in these two tables suggests that a self-selection bias may have been operating, whereby Ranch Handers who had had cancer (and potentially other conditions) were more likely to complete the examination than were comparisons. This type of self-selection is not illogical, if Ranch Handers believe that Agent Orange may have been responsible for their cancers, and are more motivated to participate in a study that might shed light on that relationship.

Based on the figures in Table 1 above, Albanese reported a statistically significant relative risk of 1.97 for all cancers combined. The data in the second table above yield a relative risk of 1.6, which is not significant. A relative risk of 1.9 for skin cancer is still statistically significant. If there really is a self-selection bias operating here, however, it could extend back to those agreeing to the interview in the first instance. If it followed the pattern associated with agreeing to the examination, it might mean that the Ranch Hands with cancer would be more likely to participate than comparisons with cancer. The excess skin cancer finding should certainly not be ignored, but it should not be overinterpreted either, and these possible biases should be taken into account.

According to the 1987 report, incidence of skin and systemic cancers during the interval between the first and second morbidity surveys was not significantly different between Ranch

Hands and comparisons. Looking at the entire followup period (combining initial incidence with interval incidence), there was again no significant difference in an "unadjusted" analysis. However, when the analysis was adjusted for varying distributions of characteristics known to affect the incidence of the predominant form of skin cancer--skin color, reactivity to the sun, occupation, latitude of residence--there was a significant excess among the Ranch Hands (relative risk of 1.56) not explainable by other known factors.

Birth Defects

A significant excess of birth defects reported by Ranch Hand parents is given considerable attention by the 1984 report and by Albanese. The Air Force has not dismissed this finding and is in the final stages of obtaining birth records for all births to all study participants. The analysis based on actual records (rather than parents' reports) will allow complete exploration of this important area. Dr. Albanese's concern is well taken, and the action by the Air Force is a comprehensive one.

Psychological Assessment

Albanese bases his report of significant adverse psychological findings on responses to questionnaires showing the Ranch Hands to be less well on the following indices: fatigue, anger, mental erosion, anxiety, isolation, and depression. The depression finding was not corroborated by responses to a test administered during the physical examination. In one case, an index of denial, the comparisons were less well, but this is not reported by Albanese, which seems arbitrary. The 1987 data show fewer differences, and the differences are split more evenly with respect to which group has the more favorable measurement. On the one specific measure designed to detect possible organic causes for psychological effects, no differences between Ranch Hands and comparisons were found. There were also no significant differences in the frequency of actual psychologic pathology, i.e., in the number of diagnosed cases of mental disorder. A reanalysis of these data using the blood dioxin levels as surrogates for exposure may prove useful in determining whether such an effect exists.

Hepatic Examination

Differences between Ranch Hand and comparisons in certain laboratory measurements were noted by the 1984 report and by Albanese. Albanese also points to a highly significant difference in the number of liver disorders other than hepatitis, jaundice, or cirrhosis reported by participants and verified in their medical records. Of the 13 reported in Ranch Hands, 10 were of an unspecified nature, making this an uninterpretable finding.

At the second examination, some shifts had taken place, and the 1987 report states that, of the measures in which there were significant differences, about half tended to favor the Ranch Hands and half the comparisons.

Cardiovascular System

The significant finding in this area was poorer peripheral pulses among some Ranch Hands. This finding was no longer significant by 1987. The researchers suggest that, in part, the lack of a difference in the later examination may be due to the participants being asked not to smoke before the examination, because smoking directly affects the vascular system. This had not been the practice during the first examination.

Endocrinologic Effects

Differences between the two groups in several laboratory measures were noted by Albanese and the 1984 report. By the second examination, at least some of these differences had disappeared, and overall, the Ranch Hands and the comparisons differed on a number of measures, some in which the Ranch Hands fared better, and some in which the comparisons fared better.

Conclusion

The report by Dr. Albanese does not call into question any of the findings reported directly by the Air Force study team in their original reports. Albanese does draw attention to the fact that the study results cannot be taken to mean that Agent Orange is not harmful, or that the Ranch Hands are entirely free of any effects. The study is limited by its size and by the relatively young age of the participants. Other than continuing to study this group, as is planned, and to use new technology to determine dioxin body burdens, the reinterpretation does not suggest interventions of any kind or new directions for AFHS.

MAY 4 1988

Honorable G. V. (Sonny) Montgomery
Chairman, Committee on
Veterans' Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

I am writing in response to your letter of March 30, 1988, requesting the Veterans' Advisory Committee on Environmental Hazards review a recently released Air Force Report prepared by Dr. Richard A. Albanese in which he evaluates the relationship between the findings of the 1984 morbidity report of the Air Force's Ranch Hand study ("United States Air Force Personnel and Exposure to Herbicide Orange") and an in-depth literature review of the toxicology of dioxin.

I have discussed your request with the Chairman of the Scientific Council, Dr. Kurland, who expressed a preference for a conference call among the Dioxin Panel members to evaluate this report. Because of the schedules of the members and the requirements of the Federal Advisory Committee Act, a conference call has been difficult to arrange. We have tentatively set May 27 as the date for the call. I shall notify you when final arrangements have been made.

I expect to have the approved minutes for the February 1988 meeting of the Advisory Committee available for distribution in the near future. I will provide you with a copy of these minutes at that time.

An identical letter is being sent to the Chairman and Ranking Minority Members of the Senate and House Committees on Veterans' Affairs who co-signed your March 30, 1988, letter. Thank you for your interest in the Committee.

Sincerely,

FREDERIC L. CONWAY
Executive Secretary,
Veterans' Advisory Committee
on Environmental Hazards

Veterans' Administration Veterans' Advisory Committee on Environmental Hazards Review of

"United States Air Force Personnel and Exposure to Herbicide Orange"
Richard A. Albanese, M.D., February 1988 (USAFSAM-TR-88-3)

MINUTES OF THE VETERANS' ADVISORY COMMITTEE ON ENVIRONMENTAL HAZARDS

May 27, 1988

Members of the Dioxin Panel of the Scientific Council of the Veterans' Advisory Committee on Environmental Hazards conferred via telephone to discuss a report by Richard A. Albanese, M.D., entitled, "United States Air Force Personnel and Exposure to Herbicide Orange." (USAFSAM-TR-88-3). The review was conducted pursuant to a request by the Chairmen and ranking minority members of the House and Senate Veterans' Affairs Committees. Because of technical difficulties, members of the public and others could not hear the telephone communication among the members. Consequently, Dr. Colton, the Chairman of the Dioxin Panel, summarized to those present the comments the various Committee members made.

Mr. Conway briefly described the events leading to the conference call, noting that he conferred with Mr. Meadows, the Chairman of the Committee, and Dr. Kurland, the Chairman of the Scientific Council, after receiving the request from the Congressional Veterans' Affairs Committees. It was agreed that the matter could not wait until the next scheduled meeting of the Committee in November. Of the several options discussed, among which were submission of written comments by Committee members, convening a meeting of the Scientific Council, or conducting a telephone conference call, it was decided that the best option was a conference call as it could be more easily scheduled and it would afford the participating members the benefit of engaging in dialogue with one another.

The abstract for the paper summarized Dr. Albanese's work as follows:

> The United States Air Force is conducting an epidemiological study, called the Air Force Health Study (AFHS), to determine whether or not military personnel associated with herbicide spraying during the Vietnam War have experienced any adverse health effects. This report reviews salient findings of the AFHS first morbidity report published in 1984, and presents new work by examining relationships between AFHS findings and the results of laboratory toxicological studies and other epidemiological studies addressing dioxin. Eleven clinical areas have been emphasized based on a toxicological profile developed from the literature and availability of data in the AFHS: weight loss, neoplasia, birth defects, neurological changes, psychological changes, hepatotoxicity, chloracne, cardiovascular changes, immunological deficits, endocrine changes, and mortality. In six of these eleven clinical areas, statistically significant group differences occurred, and in five of these six

> instances the group differences were in the direction of expected dioxin effects. Dioxin cannot be confidently identified as the causative agent of these findings at this time because of several reasons, including the absence of correlations with an exposure index and the incomplete clinical picture. However, dioxin is not exonerated as a causative agent because of the directionality of the observed group differences and the preliminary nature of the exposure index used in the AFHS first morbidity report.

Mr. Conway provided the summary comments made by Dr. Lathrop to the participating members. Dr. Lathrop characterized the report as being bad science and fatally flawed. He noted that the author made inappropriate use of outdated data to identify human end points which the author determined to be of interest. The author then inappropriately analyzed data generated from the 1984 morbidity report to fit his notion of appropriate end points. Dr. Lathorp noted, however, that the author gave no recognition to the fact that the 1984 data are no longer reflective of the current health status of the Ranch Hand group. This was a fatal flaw, in Dr. Lathrop's opinion, because many of the differences observed at the time of the 1984 report were not present in the 1987 morbidity data. Dr. Lathrop also questioned the propriety of using animal data to predict human experience in a situation such as this where there is wide species variability and human exposure data are not consistent with much of the animal exposure data. Dr. Lathrop expressed concern that in light of these critical errors, any inferences derived from this report would be erroneous.

Dr. Lathrop also observed that the author had expressed essentially the same conclusions when he issued a minority report at the time of the release of the 1984 morbidity data.

Dr. Yanders expressed agreement with Dr. Lathrop's assessment. He stated he was astonished that the author would issue a report based upon old data when new data which did not continue the earlier observed trends were available. Dr. Yanders also noted that some of the items identified by the author as having a positive association were not born out by the new data and in some instances were not even supported by the old data.

Dr. Yanders also took issue with the author for using unvalidated, self-reported data on the occurrence of birth defects among the progeny of the study population.

Dr. Sinclair and Dr. Bender expressed agreement with the views of Dr. Lathrop and Dr. Yanders. Dr. Colton noted that the author did express some caution in interpreting his study. The author never claimed that a cause and effect relationship had been established and he acknowledged the possibility of confounding variables. Dr. Bender agreed that the author only wrote in terms of trends and that no definitive conclusions had been made.

The participating members agreed that the paper was relevant to the veterans' concerns; that the conclusions may have been supported by the 1984 data but were not supported by the 1987 data; and the VA's guidelines should not be modified in light of the findings contained in this report.

Mr. Conway agreed to prepare a draft consensus statement of the Panel members' views. Upon approval, those views would be conveyed to the House and Senate Veterans' Affairs Committees.

Whereupon the telephone conference of the Dioxin Panel of the Scientific Council of the Veterans' Advisory Committee on Environmental Hazards adjourned.

APPROVED: Frederic L. Conway
f THEODORE COLTON, SC.D.
Chairman, Dioxin Panel
Scientific Council, Veterans' Advisory
Committee on Environmental Hazards

July 27, 1988
Date

Members Participating:

Dr. Bender
Dr. Colton
Dr. Sinclair
Dr. Yanders

Agency Personnel Present:

Dr. Hobson
Mr. White
Mr. Drembus
Mr. Drash
Dr. Kang

Members of the Public in Attendance: 5

Congreſs of the United States
Washington, D.C. 20510

December 8, 1987

Honorable Donald M. Newman
Chair
Agent Orange Working Group
Domestic Policy Council
2000 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Newman,

As you may know, a report on a study by Dr. Han Kang and colleagues, entitled "Soft Tissue Sarcoma and Military Service in Vietnam: A Case-Control Study", was published in the October 1987 issue of Journal of the National Cancer Institute. This study sought to "examine the association of soft tissue sarcomas (STSs) with military service in Vietnam as well as other host and environmental risk factors". According to the report, the researchers found a small, not statistically significant increase in the risk of STS among subgroups of Vietnam veterans who had higher estimated opportunities for exposure to agent orange but concluded that Vietnam veterans generally "did not have a statistically significant increased risk of STS when compared to men who had never been in Vietnam".

As the Chairmen and Ranking Minority Members of the Senate and House Committees on Veterans' Affairs, we are writing to request that the Agent Orange Working Group review and provide comments on this study. In particular, we would appreciate your evaluation of the scientific methods used and of the validity of the statistical analysis. We would also appreciate your identification of any specific findings discussed in the study which warrant follow-up investigation or analysis, especially in light of the ongoing Centers for Disease Control Selected Cancers Study, its epidemiological studies of the health of Vietnam veterans, and other pertinent studies such as the 1987 Western Washington State study, the 1986 National Cancer Institute/University of Kansas study, and the Swedish studies regarding agricultural workers.

As always, we thank you for your continuing cooperation and assistance.

With best wishes,

Sincerely,

Alan Cranston
Alan Cranston
Chairman

Frank H. Murkowski
Ranking Minority Member

Senate Committee on
Veterans' Affairs

Sonny Montgomery
G.V. (Sonny) Montgomery
Chairman

Jerry Solomon
Gerald B.H. Solomon
Ranking Minority Member

House Committee on
Veterans' Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Phone: (501) 541-4000
(FTS) 790-4611

National Center
For Toxicological Research
Jefferson AR 72079

February 16, 1988

The Honorable Donald M. Newman
Chairman, Domestic Policy Council
Agent Orange Working Group
Department of Health and Human Services
200 Independence Avenue, S.W.
Room 614-G, HHH Building
Washington, D.C. 20201

Dear Mr. Newman:

Prior to your request and in anticipation of a possible Congressional request, the AOWG Science Panel reviewed the JNCI article by Kang et al. entitled "Soft tissue sarcoma and military service in Vietnam: A case-control study" and discussed it at the November 24, 1987 Science Panel meeting. A written summary of the Science Panel reviewers' comments along with the individual responses is attached.

The Science Panel was in agreement that the study contains important information that should be published and that in general the scientific methods and statistical analysis were valid. However, there was general criticism to the authors' statements implicating Agent Orange.

I wish to thank the following individuals for taking the time to review the article and submitting written comments: Drs. Gaylor, Kodell, Chen and Young, NCTR; Dr. Vernon Houk and Staff, CEH/CDC; Col. George Stebbing, OASD/HA; Dr. Donald Barnes, USEPA; Col. William Wolfe, USAF; Dr. Carl Keller, NIEHS; and Dr. Marilyn Fingerhut, NIOSH/CDC.

If more information is needed, please do not hesitate to ask.

Sincerely,

Ronald W. Hart, Ph.D.
Chairman, AOWG Science Panel
Director, NCTR

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

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National Center
For Toxicological Research
Jefferson AR 72079

Summary of Reviews of JNCI 79 (4):693-699, 1987
Soft Tissue Sarcoma and Military Services in Vietnam:
A Case-Control Study

by

Dr. H. Kang	Dr. F. Enziger
Dr. P. Breslin	Dr. M. Feil
Dr. Y. Lee	Dr. B. Shepard

Reviews submitted by Drs. Gaylor, Kodell, Chen and Young, NCTR; Dr. Vernon Houk and Staff, CEH/CDC; Col. George Stebbing, OASD/HA; Dr. Donald Barnes, USEPA; and Col. William Wolfe, USAF.

The Congressional inquiry requests the Agent Orange Working Group to:

A. Evaluate the scientific methods used.
B. Review validity of the scientific analysis.
C. Identify findings which warrant further investigation as related to other studies.

RESPONSE

A. Scientific Methods

All reviewers mentioned the inappropriateness of the Agent Orange implications in this paper. Each cited the recently completed Centers for Disease Control (CDC) study which attempted to correlate serum levels to exposure indices as information which should have been taken into consideration. Even though the CDC study may not have been completed when the article was initially submitted to the journal, the CDC study was definitely complete when the galley proofs were returned to JNCI and then distributed to the Science Panel members.

B. Validity of the Study

Most reviewers agreed that the study is important and should have been conducted and published. However, there are several specific criticisms:

1. Several reviewers commented on the inappropriateness of the use of MOSC and military region as potential subgroups.

2. Other reviewers questioned why controls were not matched to the STS cases by race or vital status.

3. Several reviewers questioned the statement concerning the limitation of selection bias due to publicity by only considering those STS cases reported between 1975 and 1980. It was pointed out that a great deal of publicity was generated in the late '60s and early '70s concerning the environmental effects of Agent Orange and again in the late '70s when the AOWG was formed.

4. Other reviewers expressed concern that the long latency period for appearance of STS may have forced this into a negative study.

C. Conclusions, Specific Findings and Need for Clarification

Most reviewers agreed that it is unfortunate that the study was published without the input and review of the Science Panel which undoubtedly would have recommended the elimination of the controversial and unsubstantiated statements implicating Agent Orange.

Even though this and several other recent studies have not found a positive correlation between Vietnam service and STS cases, the long latency period for STS and the one positive study would indicate that this form of cancer needs to continue to be monitored along with several other cancers (specifically non-Hodgkins lymphomas).

As each reviewer stated his concerns in his own particular manner and felt some issues were more important than others, it is the Science Panel's policy to pass on the individual comments as well as this more general summary. The individual reviews are attached.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date November 18, 1987

From Drs. Gaylor, Kodell, Chen, and Young

Subject NCTR Review of JNCI 79(4):693-699, 1987

To Ronald W. Hart, Ph.D.
Director, NCTR

There is no basis for implying AO association with STS in the Abstract or in the Summary paragraph at the end of the article (entitled "Soft Tissue Sarcoma and Military Service in Vietnam: A Case-Control Study"). Even with the caveats and disclaimers of non-significance, the AO implications should not be made.

There were no statistically significant findings reported in this study. The first sentence of the Discussion section is a biased statement and should be restated; the results of this study do not support "any" association, much less a "strong positive" association between Vietnam service and the occurrence of STS.

Based on the recently completed CDC study that indicated that all attempts at catagorizing AO exposure in Vietnam were no good, the use of Military Occupation Specialty Code or military region to indicate AO exposure is without merit.

In addition, the area where the authors indicated extensive AO spraying, the OR was the lowest (Table 4, OR = 0.53).

The article would be much improved if Table 5 and all inferences to Agent Orange (AO) were removed.

It is surprising that no comparison was found to be significant as you would expect 1 or 2 comparisons to be significant by chance alone.

Table 5 also has an error in column 2 and line 1 of the data as the column and row totals do not add up. If the Military Region I Controls Yes value were 6 instead of 7, the table would balance.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

te November 23, 1987

From Director
Center for Environmental Health and Injury Control

Subject Response to Kang et al., JNCI — 12 Nov 1987

To Ronald W. Hart, Ph.D.
Chairman, AWOG Science Panel

Kang et al. (1) report no association between soft tissue sarcoma (STS) and service in Vietnam in a study of 217 STS cases and 599 controls, with an odds ratio of 0.8. However, they suggest that "veterans who had higher estimated opportunities for Agent Orange exposure seemed to be at greater risk of STS...." Recent data on serum dioxin levels in Vietnam veterans suggest that their measure of estimated opportunity for exposure is not likely to be reliable, casting doubt on the validity of this statement.

The data leading to their comment about the risk of exposure to Agent Orange are summarized in their Table 4, the heading for which describes a classification by "categories of estimated Agent Orange exposure likelihood." In fact, the Vietnam veterans are classified by military occupational specialty category (MOSC) as combat or noncombat and, for Army veterans, also by military region. Kang et al. provide no data to support their statement that veterans who saw more combat might have been more likely to be exposed to herbicides.

Data relevant to using MOSC as a surrogate for herbicide exposure are available from the Centers for Disease Control's recently completed study of serum dioxin levels in 646 Vietnam and 97 non-Vietnam male U.S. Army veterans (2). As shown in several recent studies (3-5), current serum dioxin level can be used as an objective biological marker for heavy exposure to Agent Orange in Vietnam. The 646 Vietnam veterans in the CDC study served as ground combat troops in the III Corps military region during 1967 and 1968, a time of heavy spraying. More than 80% had a combat MOSC. The distribution of their serum dioxin levels was nearly identical to the distribution of levels in the 97 veterans who did not serve in Vietnam. There was no relation between dioxin levels and self-reported intensity of combat in the Vietnam veterans. There was also no association between dioxin levels and number of days a veteran's unit spent in five heavily sprayed regions, four of which (War Zones C and D, the Iron Triangle, and Rung Sat) were heavy combat zones. In summary, the CDC study suggests that a combat MOSC is unlikely to be a better indicator of likelihood of exposure to Agent Orange than are other indicators derived from military records. As Kang et al. indicate, these other measure have been rejected as inadequate surrogates for exposure to Agent Orange.

Several other points are worth considering. Vietnam veterans with a non-combat MOSC include clerks and others who served in combat areas with combat troops. If the most likely source of exposure to Agent Orange was spraying around base camps, as has been suggested (6), these "non-combat" troops were about as likely to be exposed to Agent Orange as were those with a combat MOSC. Other plausible differences between veterans with combat and non-combat MOSC, such as education and stress, could be confounders for the associations in Table 4, but Kang et al. do not report an attempt to control for such factors.

In addition, in finding these suggested associations Kang et al. have examined particular subgroups. Standard practice requires great caution in interpreting the results of subgroup analyses, particularly (as the authors emphasize) when the association between the subgroup and the exposure of interest is very uncertain. That caution was not exercised by the quoted statement in the first paragraph of this letter.

REFERENCES:

(1) KANG H, ENZIGER F, BRESLIN P, et al. Soft tissue sarcoma and military service in Vietnam: a case-control study, JNCI 1987; 79:000-000.
(2) Centers for Disease Control. Serum dioxin in Vietnam-era veterans - preliminary report. Morbidity and Mortality, Weekly Report 1987; 36:470-475.
(3) GROSS ML, JACKSON O, LYON PA et al. 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in adipose tissue of Vietnam veterans. Environmental Research 1985; 33:261-268.
(4) KAHN PC, GOCHFELD M, RAPPE C, et al. Analysis of adipose tissue and blood samples from Vietnam veterans: project outline and preliminary results.
(5) PIRKLE JL, WOLFF WH, PATTERSON DG, et al. Estimates of half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Ranch Hand veterans. Presented at the Seventh International Symposium on Chlorinated Dioxins and Related Compounds, Las Vegas, 1987.
(6) AOWG Science Panel. Report of the Agent Orange Working Group Science Subpanel on exposure assessment, Washington, DC: Department of Health and Human Services. June 3, 1986.

Vernon N. Houk, M.D.
Assistant Surgeon General

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, D.C. 20301-1200

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15 November 1987

Comments on the article: Soft Tissue Sarcoma and Military Service 2
in Vietnam: A Case-Control Study
by Han Kang, Dr. P.H. et al.

A primary question is why was the AOWG Science Panel not given sufficient time prior to the publication of this paper in the Journal of the National Cancer Institute to provide thorough written comments to the authors and to the Chairman of the Science Panel? The letter to the Science Panel members was dated October 2, 1987 and was not received at the Department of Defense until several days later with publication being scheduled for October 9, 1987.

What peer review process did this article go through at the Veterans' Administration prior to submission to the journal for publication? Why did the Science Panel not have an opportunity to review the presumed reviewers comments?

The following comments refer to specific paragraphs of the article's galley proofs as provided by the VA letter of Oct. 2, 1987:

Page Ref	Paragraph	Comments
3	2.	Why was the study stopped in 1980 when another 5 to 6 years of information could have been obtained on STS, especially when it has such a long latent period from exposure to the carcinogen? The original controversy on herbicides began as early as 1968 in the public press around the world. This is what forced the cessation of Ranch Hand spraying in 1969.
3	3	Why were not the controls matched to STS on the basis of race or vital status?
4	3	Why were combat engineers excluded while tank crews were included? Many combat engineers cleared trees and brush which had the potential for strong residual concentrations of herbicides, especially Orange. Many other personnel not necessarily having a combat MOS were stationed on firebases and other fortified installations which had had their perimeters repeatedly sprayed with herbicides. These non-combat type troops may have had repeated exposures to spray drift situations from perimeter spraying. On the other hand tank crews being protected by their vehicles would not likely have had their uniforms and skin contaminated by any herbicide on the foliage. Why did they not include Chemical Corps troops? Were any of these STS cases Chemical Corps troops?

15 November 1987

Page Ref	Paragraph	Comments
4	5	Although III Corps did receive very heavy spraying during the entire war, many of the exact same areas were repeatedly sprayed from year to year because of the regrowth of the dense forests. On the other hand large areas where there were combat troops were never sprayed with Agent Orange because there were no dense forests to defoliate. The NAS overlay transparencies show this fact quite clearly. Thus many Army members with a combat MOS who served in III Corps may not have been serving in areas which had been intensively sprayed with Agent Orange. A very detailed tracking of each of the STS case Vietnam veterans would have to have been accomplished to make sure that they were serving in sprayed areas. We should not forgot that thousands and thousands of gallons of herbicides Blue and White were also sprayed in these areas and neither of them contained TCDD. This is a rather sloppy and inexact way of relating any herbicide exposure to these STS cases. It casts doubt on any credibility of the findings of the study. Also a mission should be differentiated from a sorte. Gallons of Herbicide Orange disseminated over a specifically defined area is a much more accurate way to determine how much Orange was laid down on the forests.
5	5	What are "non-ground troops" are they only Air Force and Navy personnel in the air or on ships? There is no way from the methodology used to even say that certain combat troops had "higher estimated opportunities for Agent Orange exposure". Also the non-combat troops, if stationed at a firebase, such as headquarters administrative or medical corpsmen personnel, may have, in fact, received higher exposure to Herbicide Orange if that firebase had been repeatedly sprayed around the perimeter with Agent Orange. At the same time those "combat troops" assigned to the firebase may have been out in the field operating in areas where there had been no spraying and away from the firebase when the permanent party personnel were exposed to perimeter spraying. A very detailed review of the whereabouts of each STS Vietnam veteran on a day-to-day basis in relation to actual spray missions and perim-

Page Ref	Paragraph	Comments
		eter spray activities before one could say that this person had a likelihood of Orange exposure.
7	1	Much was written in the public press as early as 1969 about the terrible environmental effects from herbicide spraying in Vietnam. This furor generated an extensive study done by the NAS in the period of 1972 to 1974 so this statement does not ring true. The effects on chickens was found in 1969 and this led to the cancellation of Ranch Hand spraying of Agent Orange in 1969. More research should have been accomplished on the Congressional hearings and the earlier public press articles which covered the period from the late 1960's. Concerning the health status of both STS cases of Vietnam veterans and control Vietnam veterans, was any attempt made to secure their military medical records to determine what had been their health and disease incidence while they were in the Army or Marines?
7	3	The tone of this paragraph gives one the impression that the authors are trying to seek out a positive correlation between STS and Agent Orange exposure even though the data does not support such a conclusion. Why was this even included in the discussion? There is no way that you can say that these men were more likely to have had Agent Orange exposure considering the exceptionally crude methods used to assign exposure. Since the numbers of STS cases were so small a much more detailed analysis of exposure should have been undertaken to increase the value of these findings.
12	Table 5	It is interesting to note that of the 7 cases of STS found in I Corps, 4 of these did not have a Combat MOS. Also in II Corps there were two cases and none of these soldiers had a combat MOS. Even in III Corps one case was found in a soldier with a non-combat MOS. In the total figures there were 8 cases having a combat MOS while 7 did not have a combat MOS, almost a 50/50 ratio which would seem to discount the combat MOS as a determining factor in exposure to Agent Orange. It is also very interesting to note that there were more

15 November 1987

Page Ref	Paragraph	Comments
		STS cases (7) in I Corps in Army troops than there were in III Corps (6). I Corps had the next to lowest number of spray missions recorded as per page 4, paragraph 5. Add to this the five Marine cases of STS and the concentrations of STS cases are much higher in I Corps than in III Corps where all the spraying was supposed to have taken place. It just does not make sense to draw any conclusions as to Agent Orange exposure in III Corps from the data found. Were any comparisons made as to the total numbers of Marine Corps and Army troops concentrated in the four Corps areas. The results may have been more closely related to sheer numbers of troops located in each of the Corps areas and have nothing to do with either a combat MOS or Agent Orange exposure.

COMMENTS ON THE SOFT TISSUE SARCOMA STUDY

1. The authors comment that Hardell (references 5 and 6) found an increased risk of STS in exposed persons. The study was a case control design, that found increased exposure in patients with STS. Technically, the study found an increased "risk" of exposure in STS patients, not an increase of STS in an exposed cohort.

2. The authors' assumption that Agent Orange was the exposure of interest is inappropriate in light of the CDC study of serum dioxin levels in ground troops.

3. In page 3, para 2, the authors infer that there was no publicity on the effects of Agent Orange prior to 1980. In fact, intense publicity began in 1978, and the Hardell studies began to appear in 1979. Selection bias could have occurred between 1978 and 1980. 1978 should have been the cutoff point for selection of cases in this study.

4. The authors need to clarify the criteria used for selection of controls. Were the same criteria used in all facilities submitting specimens to AFIP for the study?

5. A table of the distribution of diseases in the controls should be provided.

6. The comments on Agent Orange exposure on page 4 are misleading in view of the low levels of dioxin found in ground troops by the CDC study. Agent Orange exposure should not be presented as a cause of any observed findings.

7. The discussion of results on page 5 needs to be expanded to place the observed odds ratios (OR) in better perspective. It is misleading to emphasize a nonsignificant OR with a broad confidence interval (that includes 1) because it fits the study hypothesis. It is likely that the reader who is not an epidemiologist or statistician will misinterpret the discussion.

8. The use of the adjective "strong" in the phrase "does not support a strong positive association" on line 2, para 1 of page 6 is also misleading. The data do not demonstrate any positive association. The OR were all nonsignificant. The authors appear to have overinterpreted the subgroup analyses ---- the confidence intervals of the odds ratios included 1, and the likelihood of significant exposure to Agent Orange in these men is highly questionable.

William H. Wolfe, Col, USAF, MC
Chief, Epidemiology Division

AOWG Science Panel, November 17, 1987. Carl A. Keller,Ph.D. NIEHS

"Soft Tissue Sarcoma and Military Service in Vietnam:
A Case-Control Study"
Han Kang, et al, JNCI 79, 693-699, 1987.

A comparison of 217 cases of Soft Tissue Sarcoma diagnosed at the AFIP with 599 controls from the same referral sources revealed that Vietnam veterans were at no greater risk from this cancer than men who had never been in Vietnam. The study was designed to have 98% probability of detecting a twofold increased risk of STS among Vietnam veterans had such an elevated risk existed. Markedly elevated risks were found for Army and Marine Vietnam veterans who held combat-related Military Occupational Specialty Codes (i.e., infantry, field artillery, etc.) or were assigned to one of the 2 Military Areas in Vietnam where much Agent Orange was known to have been used. These elevated risks, however, were based on relatively small numbers and did not test as statistically significant. Cases and controls were identified between 1975 and 1980 to avoid spurious association following publication of the Swedish data linking STS to phenoxyacetic acid containing herbicides. Other possible biases due to the source of case material seem to have been adequately disposed of.

The study appears to have been well designed and well executed and apparently indicates that Vietnam veterans are at no greater risk from STS than others. However, several additions and changes in the data which is presented might make it easier to interpret the results. There should have been a comparison of Vietnam veterans to other veterans as well as to non-veterans. Do veterans have a different risk for STS? Do Vietnam veterans with the longer [among admittedly short] possible latency periods have a different risk? It can be calculated from Table 4 that, compared to other veterans among the "ever in Vietnam", Army and Marine veterans have an estimated relative risk for STS of only 0.50 which is of borderline statistical significance (Chi Sq.= 4.02, uncorrected for continuity). Thus, if combat Army and Marine veterans have twice the risk for STS as non-combat Army and Marine veterans from Vietnam, (as can be calculated from Table 5) they must have about the same risk as other Vietnam veterans (presumably Navy and Air Force). This suggests that results in no way support any association between STS and Agent Orange exposure, even non-statistically significant. In addition, although the narrative states that "No statistically significant association was found between STS and other study variables" the data in Table 6 clearly indicate that cigarette smokers were at significantly lower risk from STS than non smokers. How this is related to the Vietnam veteran issue cannot be determined without some form of multivariate analysis of the data, of which there is no evidence in the manuscript.

In summary, while the study seems to have been well done, the published report makes more mention of the possible role of Agent Orange than the results which are presented can support. The results which are presented "do not support"...[any]..."positive association between Vietnam service and the occurrence of STS."

Comments on "Soft Tissue Sarcoma and Military Service in Vietnam: A Case - Control Study" JNCI 79:693,1987

M. Fingerhut

November 20, 1987

This case-control study utilized STS pathologic specimens sent to the Armed Forces Institute of Pathology between 1975 and 1980 for men born between 1940 and 1945. Controls were obtained from patient logs of referring pathologists. Vietnam service was determined by review of military records. Analysis was conducted by calculating the Odds Ratio for the entire study group and for subgroups suggested to have possible Agent Orange exposure. No statistically significant increased risk for STS was found in the Vietnam veterans or in the Agent Orange subgroups.

The study seems to have been conducted properly, and the results were presented clearly in the JNCI article. The authors considered carefully all possible sources of bias in the Discussion section.

Several points come to mind regarding the desirability of coordination of research studies at the Veterans Administration:

1. Did the authors of this article know the results of the CDC Validation study prior to submitting this article to JNCI? If so, the sections on Agent Orange estimates should have been revised to reflect the CDC findings that ground troops did not have substantial exposure.
2. This article states clearly that Military Region III received the heaviest Agent Orange spraying (3,487 spray missions), but the V.A. Mortality Study suggested that Military Region I received the heaviest spraying. If that report is revised, it is desirable to have the report be consistent with this report. It should also reflect the results of prior studies such as the CDC Validation Study.
3. This case control study has some overlap with the Irey study of STS pathologic specimens. The Irey report should clarify similarities and differences in the two studies.

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Congress of the United States
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WASHINGTON, DC 20510-8025

JOHN H. GIBBONS
DIRECTOR

FEB 11 [illegible]

February 4, 1988

The Honorable G.V. Montgomery
Chairman
Committee on Veterans' Affairs
U. S. House of Representatives
Washington, D.C. 20515

Dear Sonny:

Enclosed is a Staff Paper prepared by the OTA Health Program, reviewing the study, "Soft Tissue Sarcoma and Military Service in Vietnam: A Case Control Study," by Han Kang, Franz Enziger, Patricia Breslin, Michael Feil, Yvonne Lee, and Barclay Shepard, in response to the letter you and your colleagues sent me on December 8, 1987.

The study was basically well designed and well executed, and it had greater statistical power than any previous studies of soft tissue sarcoma (STS) in Vietnam veterans. Their finding of no increased risk of STS among Vietnam veterans as a group is very strong, and is unlikely to be a spurious result. We do not believe, however, that this study provides support for increased risk of STS among subgroups of veterans. None of the subgroup analyses were statistically significant, therefore the point estimates of risk were very imprecise. In addition, the recent CDC "validation study" provided evidence that few ground troops, regardless of the nature of their military activities in Vietnam, had significant exposure to Agent Orange. The CDC study was undertaken because categorizations such as were used in this VA study were inadequate bases for epidemiologic studies.

The findings of the Swedish forestry worker studies, in light of CDC's validation study findings, appear to have lesser relevance for Vietnam veterans, particularly ground troops. In addition, the STS-phenoxyherbicide hypothesis has not generally been corroborated by other studies. The Swedish studies still stand as the major support for the hypothesis.

The CDC Selected Cancer Study, which includes STS, is gathering cases from a later time period, (July 1984 through June 1988), which could conceivably provide evidence of an increased risk with a longer latency period. The CDC STS study will have roughly the same power as this VA study. Although CDC will accrue more STS cases, according to their original estimates, a smaller proportion of the underlying population will be veterans, which is the major determinant of the study's power in this case.

If CDC's case control study has findings similar to this VA study regarding STS, there will be no reason to continue considering the possibility that STS could be a major problem for Vietnam veterans. This is not equivalent to saying that phenoxyherbicides do not cause soft tissue sarcoma, as the final judgment on that connection cannot yet be made, nor that there might not be a small number of STS cases arising in Vietnam veterans with some relationship to their military service. But, in the absence of positive evidence, any excess risk must be quite small.

I hope you and your colleagues find this analysis helpful. Please do not hesitate to call me if I may be of further assistance, or contact Hellen Gelband, in the OTA Health Program (at 8-6590), who was responsible for this review.

Sincerely,

Jack

John H. Gibbons

enclosure

OFFICE OF TECHNOLOGY ASSESSMENT CRITIQUE OF THE PAPER:

"Soft Tissue Sarcoma and Military Service in Vietnam: A Case Control Study"

by Han Kang, Franz Enziger, Patricia Breslin,
Michael Feil, Yvonne Lee, and Barclay Shepard
(Journal of the National Cancer Institute 79(4):693-399)

Staff Paper

Prepared by Hellen Gelband

Special Projects Office of the Health Program

Office of Technology Assessment
U.S. Congress

February 1988

The views expressed in this Staff Memorandum do not
necessarily represent the views of the Technology
Assessment Board or its individuals members.

OTA Critique of:

"Soft Tissue Sarcoma and Military Service in Vietnam:
A Case Control Study"
by Han Kang, Franz Enziger, Patricia Breslin,
Michael Feil, Yvonne Lee, and Barclay Shepard
(Journal of the National Cancer Institute 79(4):693-399)

Purpose of Study

This study was conducted by Veterans Administration (VA) researchers to determine whether veterans of the Vietnam conflict were more likely to develop a soft tissue sarcoma (STS) than were men who did not serve in Vietnam. As well as using service in Vietnam as a basis for analysis, the investigators also attempted to analyze STS risk for subcategories of veterans, using measures presumed to be surrogates for Agent Orange Exposure.

Study Description

This study used a case control design. Four hundred forty STS pathology specimens referred to the Armed Forces Institute of Pathology (AFIP) in men who were of draftable age during the Vietnam conflict (born 1940 through 1955) and diagnosed during the period 1975 through 1980 formed the initial pool of cases. AFIP is well known in the pathology community for its expertise in the sometimes difficult classification of STS. According to the VA authors, one-quarter to one-third of all STS in the United States, both in the civilian and veteran population, are referred to AFIP for confirmatory diagnoses. For each case, the hospital that had referred the case to AFIP was contacted (a total of 368 hospitals) and asked to supply medical records for the STS patients and to select three male patients from their records who were born between 1940 and 1955 to serve as controls.

The number of participants finally included in the study was diminished signficantly to 217 cases and 599 controls, owing mainly to inability or unwillingness of hospitals to cooperate with the study, and also due to refusal of interviews (either by treating physicians or by the individuals or their proxies) and inability to locate some people.

All willing participants (either the chosen individuals or their proxies) were interviewed by telephone and asked a broad range of questions about their medical history, occupation and military experience, and lifestyle factors. Military history was verified by examining Department of Defense personnel service records.

Findings

Forty-five of the cases and 145 of the controls had served in Vietnam. Service in Vietnam was not associated with an increased risk of STS. This finding was quite strong, and is highly unlikely to represent a spurious finding. The study had very high power to detect a 2-fold increase in risk, and had good power to detect a 1.5-fold increase. Some corroboration for the overall null finding is the additional fact that the distribution of STS tumor types, of which there are many, was similar in the Vietnam veterans and the rest of the case group. If there were an association of Vietnam service with STS, it would most likely occur among one or a limited number of tumor types, and not across the range of types.

A number of subanalyses were carried out placing Vietnam veterans into presumptive Agent Orange exposure categories based on the following service characteristics: military occupation specialty code (MOSC; combat-related specialties treated as entailing higher probable exposure), area of Vietnam in which a man served (I, II, III, or IV Corps), and branch of service. The assumptions about relative probability of exposure related to these characteristics, and therefore the analyses based upon them, are unsupported, given current evidence. The CDC "validation study," in particular, provided evidence that few ground troops, regardless of their military activities in Vietnam, had significant Agent Orange exposure. The CDC study was undertaken because categorizations such as were used in this VA study were inadequate bases for epidemiologic studies. This is the main aspect of the VA study that can be faulted. In any case, no significant increased risks were found in the subanalyses.

Significance of the Findings

This study is the most powerful, best designed and executed study to date of STS in Vietnam veterans. The state mortality studies that have been completed (New York, Massachusetts, West Virginia) are of much weaker design, and include far fewer cases. In addition, the use of AFIP-confirmed cases alleviates the problem of misdiagnosis, which is a frequent problem with this tumor type. (In the recent study of STS in Western Washington State, 20 percent of cases originally classified as STS were actually other tumors.) The time period of the study, 1975 through 1980, is reasonable as a first period during which increased risk might become apparent, if it is, in fact, there. The CDC Selected Cancer Study, which includes STS, is looking at a later time period, July 1984 through June 1988, which should provide evidence of whether there is an increased risk but with a longer latency period. The CDC STS study will have roughly the same power as this VA study. Although CDC will accrue more STS cases, according to their original estimates, a smaller proportion of the underlying population will be veterans, which is the major determinant of the study's power in this case.

The authors of this study suggest that their results leave open the possibility of increased STS risk among subgroups of veterans. While no study can prove that no risk exists, particularly among subgroups, we believe the authors overstated the implication that even slight support for such an increased risk exists in this study. None of the subgroup analyses had significant results, and each was based on very few cases. The 95 percent confidence intervals (the range in which it is likely the "true" level of risk is included) are very wide, making the point estimates of risk (the odds ratios reported) have little practical meaning.

This study is consistent with CDC's validation study, which provided evidence that Agent Orange exposure was not widespread among ground troops, therefore one would not expect herbicide-related effects to be prevalent among these men. The STS-phenoxyherbicide link itself is somewhat weaker than it was in the early 1980's when the results of the Swedish forestry worker studies first suggested the association. The two recent studies in the United States, of STS and lymphomas in Kansas and in western Washington State, both have positive findings for non-Hodgkin's lymphomas, but have failed to confirm the connection with STS. If CDC's case control study has findings similar to this VA study regarding STS, there will be no reason to continue considering the possibility that STS could be a major problem for Vietnam veterans. This is not equivalent to saying that phenoxyherbicides do not cause soft tissue sarcoma, as the final judgment on that connection cannot yet be made, nor that there might not be a small number of STS cases arising in Vietnam veterans with some relationship to their military service. But, in the absence of other positive evidence, any excess risk must be quite small.

Office of General Counsel Washington D.C. 20420

Veterans Administration

MAY 25 1988

In Reply Refer To:

Honorable G. V. (Sonny) Montgomery
Chairman, Committee on
Veterans' Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

You had requested that the Veterans' Advisory Committee on Environmental Hazards review and comment upon a paper by Kang, et al., entitled, "Soft Tissue Sarcoma and Military Service in Vietnam: A Case-Control Study," which was published in the Journal of the National Cancer Institute (vol. 79, pp. 693-699 (1987).)

The Committee reviewed this paper at its most recent meeting in February 1988. The Committee's evaluation of this study may be found on pages 22 and 23 of the minutes of February 18, 1988. (A copy of these minutes and the minutes for the meeting of February 19, 1988, are enclosed).

An identical letter is being sent to the Chairman and Ranking Minority Members of the Senate and House Committees on Veterans' Affairs.

Sincerely,

Frederic L Conway

FREDERIC L. CONWAY
Executive Secretary,
Veterans' Advisory Committee on
Environmental Hazards

Enclosures

VETERANS' ADMINISTRATION VETERANS' ADVISORY COMMITTEE ON ENVIRONMENTAL HAZARDS
REVIEW OF

**"Soft Tissue Sarcoma and Military Service in Vietnam:
A Case Control Study"
by Han Kang, Franz Enziger, Patricia Breslin,
Michael Feil, Yvonne Lee, and Barclay Shepard**
(Journal of the National Cancer Institute 79(4):693-399)

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This study was conducted by Veterans Administration (VA) researchers to determine whether veterans of the Vietnam conflict were more likely to develop a soft tissue sarcoma (STS) than were men who did not serve in Vietnam. As well as using service in Vietnam as a basis for analysis, the investigators also attempted to analyze STS risk for subcategories of veterans, using measures presumed to be surrogates for Agent Orange Exposure.

Study Description

This study used a case control design. Four hundred forty STS pathology specimens referred to the Armed Forces Institute of Pathology (AFIP) in men who were of draftable age during the Vietnam conflict (born 1940 through 1955) and diagnosed during the period 1975 through 1980 formed the initial pool of cases. AFIP is well known in the pathology community for its expertise in the sometimes difficult classification of STS. According to the VA authors, one-quarter to one-third of all STS in the United States, both in the civilian and veteran population, are referred to AFIP for confirmatory diagnoses. For each case, the hospital that had referred the case to AFIP was contacted (a total of 368 hospitals) and asked to supply medical records for the STS patients and to select three male patients from their records who were born between 1940 and 1955 to serve as controls.

20.

Agent Orange Related Materials

The meeting was then turned over to Dr. Colton, Chairman of the Dioxin Panel.

The first paper discussed was by Del Corno, et al., "Problems in the Assessment of Human Exposure to Tetrachlorodibenzodioxin (TCDD): The Marker Chloracne." (J. Epidemiol. 1: 139-144 (1985).) This paper, as the title indicates, discussed the possible use of chloracne as an indicator of human exposure to TCDD utilizing Seveso as the source for data. The authors concluded that the assessment of human exposure from the epidemiological standpoint is a multidimensional problem and the exhaustive clinical evaluation of the health status of individuals plays a fundamental role without disregarding the usefulness of detailed information on chosen cases and their related aspects. The marker chloracne plays the role of the only clinical sign so far observed in a large group of an exposed population. For these reasons, mapping zones on the basis of chloracne cases was necessary as a complementary information supporting the description of soil contamination given by the chemical data.

Dr. Melvin, the principal reviewer, had several problems with this paper. First, he had grave doubts about the statement found in the paper, "chloracne is always associated with the presence of the toxic compounds at the systemic level (but not vice-versa)." He also had reservations about the statement, "the damage to target organs becomes evident only if the degree of intoxication at the systemic level exceeds certain thresholds." He indicated that he knew of no study in any species of animal involving both sexes which had been replicated which indicated the level of absorption at the cellular level which produced a manifest impact. He also disagreed with the statement that the kind of exposure may be one of the determinant factors. He noted that factors independent of exposure to chloracnegins per se may include age and sex.

Dr. Melvin presented a number of slides taken at Seveso, Italy after the 1976 accident at which a runaway reaction occurred followed by the dispersion of products beyond the perimeter of the plant in which the accident occurred. He noted that there were a number of irritants in the materials that were released. He presented some slides showing the development of chloracne at various stages in children and adults. He commented that a number of people stayed in the most heavily affected zone for some two weeks after the accident during which they remained in contact with dioxin and other toxic compounds, including consumption of food and animals. He also noted that many times it had been stated that several thousands of animals had died as a result of this accident. He explained, however, that many of these animals were sacrificed after the accident and that there were not that many that were known to have died from dioxin intoxication.

Dr. Melvin, in commenting further on the Del Corno paper, stated that the use of chloracne as a marker of TCDD absorption is probably justified under certain circumstances but a number of other factors need also be considered. Furthermore, he noted that there is no particularly high level of specificity for chlorance development following TCDD exposure as there are a number of compounds that may also lead to the formation of lesions of chloracne.

Dr. Lathrop, the second reviewer, commented that he too had a problem with the notion that chlorance is necessarily a marker of exposure, that in his judgment chloracne is not an absolute requirment.

In response to an inquiry by Dr. Upton, Dr. Melvin stated that there was no known information about what threshold levels would be required to produce chloracne. He observed that one of the problems was that exposure to TCDD alone probably had not occurred in industry in any circumstance. In all of the accidental exposures, there had been multiple or simultaneous or concurrent exposure to other compounds.

The overall assessment of the Committee was that the study was applicable to the veterans' experience, that the conclusions may perhaps be supported by the data but that the VA's guidelines need not be modified.

Next, the Committee reviewed the paper by Susskind, "Chloracne, 'the hallmark of dioxin intoxication'," Scand. J. Work Environ. Health 11: 165-171 (1985). In this paper, the author discussed the kind of chlorinated hydrocarbon work exposures which resulted in chlorance and the author's own experiences with TCDD exposed populations including the frequency and severity of chloracne as a subacute or subchronic manifestaion of intoxication. It was his conclusion that "choloracne is indeed a hallmark not only of TCDD absorption and bilogical response in humans, but it also a hallmark of TCDD intoxication."

Dr. Lathrop noted that Dr. Susskind did a very fine job of emphasizing the fact that production workers have the highest incidence of chloracne whereas populations of pesticide applicators and so forth, including the Ranch Hand population, have never been found to have chloracne. He commented that if in fact chloracne is a hallmark indicator for chronic symptroms such as cancer and so forth, that clearly sets forth the hierarchy for expectations wihthin the various exposed population groups. Dr. Melvin observed that this paper did not present any new data. Consequently, the Committee did not believe that the paper presented any basis for changing the VA's guidelines.

The next paper reviewed was Kang et al., "Soft Tissue Sarcoma and Military Service in Vietnam: A Case-control Study," JNCI 79: 693-699 (1987). The authors selected cases of soft tissue sarcoma from among those reported to the Armed Forces Institute of Pathology (AFIP) which involved men diagnosed between January 1975 and December 1980 who were born between 1940 and 1955, thereby restricting the study to individuals who were potentially at risk of exposure to Agent Orange and to reduce selection bias as the cut off year was before much publicity appeared concerning Agent Orange and Vietnam service. There were 217 cases of soft tissue sarcoma selected and 599 controls. Among factors looked at were Vietnam service, occupational and nonoccupational exposure to various chemicals, occupational history, medical history, and life style.

The authors concluded that the results did not support a strong positive association between Vietnam service and the occurrence of soft tissue sarcoma. Vietnam veterans as a group as well as subgroups who were categorized as having had higher opportunities for Agent Orange exposure by virtue of their military occupation or the location of their units in Vietnam did not have a statistically increased risk of soft tissue sarcoma when compared to men who had never been to Vietnam. Because the Vietnam veterans who had higher opportunities for Agent Orange exposure appeared to have greater risk of soft tissue sarcoma, the possibility of a modestly increased risk could not be ruled out. The authors noted, however, that the conclusion with respect to subgroups of Vietnam veterans was based upon a considerably weaker study power than the conclusion about Vietnam veterans in general.

Dr. Colton, the principal reviewer, noted that a major strength of the study was the scource of the cases, the AFIP, where there was an assurance of accurate diagnosis of soft tissue sarcoma. A potential weakness of the study, however, was the selective nature of the sole source of case selection. Dr. Colton also observed that this study suffered the major disadvantage of an inability to determine exposure to Agent Orange accurately. He noted that authors' statement that "Although desirable, a valid and precise estimate of the exposure of each Vietnam veteran to Agent Orange is not considered feasible based on either military records or self-reported exposure." He also commented concerning the sub group analysis of the Vietnam veterans, that the observed tendency towards increased risk was not statistically significant and suffered the limitations of an a posteriori subgroup analysis. He considered this to be a well done negative study on Vietnam service and the occurrence of soft tissue sarcoma.

Dr. Lathrop agreed that this is was a well done study and that the data were well presented.

Overall, the committee believed that they study was applicable to the veterans' experience, that the conclusions were supported by the data and that the VA's guidelines need not be modified at this time.

Dr. Bender briefly commented upon several papers as sole reviewer. He had not much to say about the paper by Jensen, "Polychlorobiphenyls (PCBs), Polychlorodibenzo-p-Dioxins (PCDDs) and Polychlorodibenzofurans (PCDFs) in Human Milk, Blood, and Adipose Tissue." (The Science of the Total Environment 64: 259-293 (1987)P) primarily because he had not been provided with a complete copy.

A second paper, "Alternatives to Using Human Experience in Assessing Health Risks" by Rall, et al., (Ann. Rev. Public Health 8: 355-85 (1987)) he noted was simply a review of national toxicology programs, strategies, and methods and so forth. He did not believe it to be pertinent to the issues before the Committee.

The last paper commented on by Dr. Bender was by Paustenbach, et al., "A Critical Examination of Assumptions Used in Risk Assessments of Dioxin Contaminated Soil." (Regulatory Toxicology and Phramacology 6: 284-307 (1986).) This paper discussed the Centers for Disease Control's risk assessment of one part per billion of 2,3,7,8-TCDD in soil which it described as a reasonable level at which to begin consideration of action to limit human exposure for contaminated soil. It also noted that the Environmental Protection Agency functionally implemented this as a standard for clean up regardless of the circumstances at the site of contamination, particularly in Missouri. The authors suggested specific alternative assumptions which, in their judgment, appeared to be more consistent with the data currently in the scientific literature.

Dr. Bender also commented on an article appearing in the January 27, 1988, Wall Street Journal which reported that the CDC and the EPA were changing their safety standards. Dr. Bender questioned the accuracy of the statement in the article that an EPA staff report argued that dioxin isn't as potent as previously believed and suggested that the risk factor for it be reduced by a factor of 16 and that the CDC was considering downgrading its assessment of dioxin risk by a factor of 20. Dr. Bender noted that the argument is not that dioxin is less hazardous but rather that it may not be necessary to clean up dioxin contaminated areas as thoroughly as had been previously required by their somewhat arbitrary limits. The Paustenbach paper described a number of factors that should be taken into account in arriving at a risk assessment, such as the ages of the individuals most likely to be exposed, the duration of the likely exposures and the methods of exposure. Dr. Bender did not think that the paper was particularly pertinent to the work of the Committee.

Justice Zimmerman next discussed a paper by Abraham and Merrill, Scientific Uncertainty in the Courts," Issues in Science and Technology, Winter, 1986, pp. 93-107. The article notes that there are three judicial stances taken toward uncertainty: confrontation in which courts face scientific issues directly and purport to resolve them on their merits; avoidance in which the courts resolve the dispute without addressing the scientific controversy; and deference in which the courts defer to another authoritative decision maker, such as a regulatory agency. The authors noted that in tort cases, the courts have less room in which to manuever so as to avoid directly confronting the scientific issue posed in a case. In this instance, burdens are created that one party or the other to the litigation must meet. Traditionally the burden of proof has rested with the plaintiff but in recent years courts have fashioned burden shifting techniques. Justice Zimmerman did not think that the paper was particularly relevant to the Committee's work. He did note that in a pragmatic way it showed the importance of the Committee's work as it assessed the evidence from all points of view. To the extent that it can be demonstrated that an Agency has considered the scientific evidence in a dispassionate way, the more likely it is that a court would give deference to the Agency's conclusions about the scientific evidence.

There then followed a brief discussion about an opinion by Judge Jenkins concerning the liability of the United States for injuries allegedly caused by its handling of the atomic weapons testing program.

Prior to adjourning for the day, the Committee members discussed the date for the next meeting of the Committee. It was agreed that the Committee would meet on November 3 and 4, 1988.

Whereupon the Committee adjourned for the day.

APPROVED: Frederic L. Conway
f. OLIVER MEADOWS
Chairman

May 23, 1988
Date

Members in attendance:

Dr. Bender
Col. Bonner
Dr. Colton
Mr. Conroy
Dr. Lathrop
Mr. Meadows
Dr. Melvin
Dr. Sinclair
Dr. Upton
Dr. Webster
Dr. Yanders
Justice Zimmerman

Mr. Murphy, Committee consultant

Public attendees: 6

Agency personnel in attendance:

Ms. Arrington
Mr. Conway
Mr. Drash
Dr. Hobson
Dr. Kang
Ms. Orr

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ALAN CRANSTON, CALIFORNIA, CHAIRMAN

SPARK M. MATSUNAGA, HAWAII
DENNIS DeCONCINI, ARIZONA
GEORGE J. MITCHELL, MAINE
JOHN D. ROCKEFELLER IV, WEST VIRGINIA
BOB GRAHAM, FLORIDA

FRANK H. MURKOWSKI, ALASKA
ALAN K. SIMPSON, WYOMING
STROM THURMOND, SOUTH CAROLINA
ROBERT T. STAFFORD, VERMONT
ARLEN SPECTER, PENNSYLVANIA

JONATHAN R. STEINBERG, CHIEF COUNSEL/STAFF DIRECTOR
ANTHONY J. PRINCIPI, MINORITY CHIEF COUNSEL/STAFF DIRECTOR

United States Senate
COMMITTEE ON VETERANS' AFFAIRS
WASHINGTON, DC 20510-6375

October 16, 1987

Honorable Donald M. Newman
Chair
Agent Orange Working Group
Domestic Policy Council
2000 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Newman,

As you may know, a report on a study by Dr. James S. Woods and colleagues, entitled "Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to Phenoxy Herbicide and Chlorinated Phenol Exposure in Western Washington", was published in the May 1987 issue of The Journal of the National Cancer Institute. The findings outlined in this report indicate that certain occupational activities involving extended periods of exposure to phenoxy herbicides used in combination with other chemicals resulted in a greater risk for developing non-Hodgkin's lymphoma, but led to no increased risk for developing cancer as a result of exposure to any specific phenoxy herbicide product alone.

As the Chairmen and Ranking Minority Members of the Senate and House Committees on Veterans' Affairs, we are writing to request that the Office of Technology Assessment review and provide comments on this report. In particular, we would appreciate your evaluation of the scientific methods used and of the validity of the statistical analysis. We would also appreciate your identification of any specific findings discussed in the report which warrant follow-up investigation or analysis, especially in light of the ongoing Centers for Disease Control epidemiological studies of the health of Vietnam veterans and other pertinent studies such as the 1986 National Cancer

Institute/University of Kansas study and the Swedish studies regarding agricultural workers.

As always, we thank you for your continuing cooperation and assistance.

With warm regards,

Cordially,

Alan

Alan Cranston
Chairman

Frank H. Murkowski
Ranking Minority Member

Senate Committee on
Veterans' Affairs

Sonny Montgomery

G.V. (Sonny) Montgomery
Chairman

Gerald B.H. Solomon
Ranking Minority Member

House Committee on
Veterans' Affairs

THE UNDER SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

NOV 27 1987

The Honorable G. V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515-6335

Dear Mr. Chairman:

This is to acknowledge receipt of your letter of October 16, 1987, requesting comments on the study by Dr. James A. Woods and colleagues, entitled "Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to Phenoxy Herbicide and Chlorinated Phenol Exposure in Western Washington".

A response will be provided to you as soon as possible.

Thank you for bringing this matter to my attention.

Sincerely,

Don M. Newman
Under Secretary

FEB 9 1988

THE UNDER SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JAN 20 1988

The Honorable G.V. (Sonny) Montgomery
Chairman
House Committee on Veterans' Affairs
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

As promised in my last letter to you dated November 27, 1987, enclosed is the review you requested of the study by Dr. James S. Woods entitled "Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to Phenoxy Herbicide and Chlorinated Phenol Exposure in Western Washington". I requested the Science Panel of the Domestic Policy Council Agent Orange Working Group (DPC/AOWG) to conduct an in-depth review of this study and I am appending the summary report from Dr. Ronald Hart, Director, National Center for Toxicological Research, who chairs the Science Panel.

In addition, the individual comments of key members of the Science Panel are included. As you will note, the specific findings discussed in the report which warrant follow up investigation and analysis are identified.

Should you have further questions, please do not hesitate to contact us.

Sincerely,

Don Newman
Chairman
Domestic Policy Council
Agent Orange Working Group

Enclosures

cc: Dr. Ralph Bledsoe, DPC
Dr. William Graham, OSTP
Mr. Gary Bauer, OPD
General Thomas Turnage, VA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Phone (501) 541-4000
(FTS) 790-4611

National Center
For Toxicological Research
Jefferson AR 72079

December 23, 1987

The Honorable Donald M. Newman
Chairman, Domestic Policy Council
 Agent Orange Working Group
Department of Health and Human Services
200 Independence Avenue, S.W.
Room 614-G, HHH Building
Washington, D.C. 20201

Dear Mr. Newman:

In response to your request, the AOWG Science Panel has reviewed the 1987 JNCI article by Woods et al. The AOWG summary response as well as the individual Science Panel members' responses are attached.

I wish to thank the following individuals for taking the time to review the article: Dr. Vernon Houk (CEH/CDC), Dr. Marilyn Fingerhut (NIOSH/CDC), Dr. Han K. Kang (VA), Dr. Carl A. Keller (NIEHS), and Col. William H. Wolfe (USAF).

If more information is needed, please do not hesitate to ask.

Sincerely,

Ronald W. Hart

Ronald W. Hart, Ph.D.
Chairman, AOWG Science Panel
Director, NCTR

AOWG Science Panel
Summary Review

Prepared by Dr. John F. Young (NCTR)
December 14, 1987

Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. J.S. Woods, L. Polissar, R.K. Seveson, L.S. Heuser and B.G. Kulander, JNCI 78(5):899-910, 1987.

Contributions to this summary review were made by Dr. Vernon Houk (CEH/CDC), Dr. Marilyn Fingerhut (NIOSH/CDC), Dr. Han K. Kang (VA), Dr. Carl A. Keller (NIEHS), and Col. William H. Wolfe (USAF). Their individual reviews are attached.

This all male study compares the occupational experience of 128 soft tissue sarcoma (STS) and 576 non-Hodgkin's lymphoma (NHL) cases and 694 controls in 13 countries of Western Washington State. Cases were diagnosed between 1981 and 1984 and were identified through a population based tumor registry and group matched by vital status and age to randomly selected controls from the same population. Study subjects were interviewed for life-time residential, military and medical histories and occupational exposures to herbicides, chlorophenols and other chemicals. These STS cases were reviewed for accuracy of diagnoses, and the study seems to have been conducted using standard epidemiological principles for case-control studies. (Keller)

In general it was felt that the study seemed to be well executed. However, there were deficiencies in the published report which made it impossible to evaluate some important issues. Specific criticisms were voiced as follows:

1. It is not clear how individuals' exposures were identified. (Keller and Fingerhut)

2. Concern about the adequacy of exposure information from interviews of next-of-kin. (Fingerhut and Kang)

3. Some subgroup differences could be due to chance alone. (Keller and Fingerhut)

4. There was some concern about the controls. (Kang and Fingerhut)

No trend of increasing risk of STS or NHL was observed for exposure to either phenoxyherbicides or chlorophenols. Subgroup analyses for specific occupational groups also showed no excess risk for STS [except lumber graders with potential exposure to chlorophenols] but did show increased risk for NHL among farmers and forestry herbicide sprayers. (Houk)

The only result in this study which is suggestive of a causal association is the statistically significant elevated odds ratio of NHL for those with 15 years exposure to phenoxyherbicides more than 15 years before diagnosis. Unfortunately, the authors did not include any details of how this was measured nor how many persons or what kinds of occupations were involved. (Keller)

There was a long discussion of why these results fail to support the positive findings from Sweden, focusing principally on shorter and more intensive exposure in Sweden vs. longer, more intermittent exposure yielding lower body burdens in Washington, but this was very conjectural. This study does not support the thesis that exposure to Agent Orange as it occurred in Vietnam is associated with NHL or STS. (Houk)

In summary, the results of this study do not support an association between STS and NHL and occupational exposure to phenoxyherbicides or chlorophenols. They do suggest, however, that a latency period of at least 15 years must ensue before elevated risks for lymphoma can become apparent. Although this fact has often been pointed out, it may not have been accorded the emphasis which is due. Perhaps the results of some other studies should be reappraised in this light. (Keller)

Comments on "Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to Phenoxy Herbicide and Chlorinated Phenol Exposure in Western Washington" by James S. Woods et. al.

M Fingerhut
December 1, 1987

It is difficult to draw conclusions from only a reading of the paper regarding the adequacy of the results, because the authors did not provide detailed information on some aspects of data collection and analysis.

For example:

1. Adequacy of Controls

   A description and discussion of the adequacy of telephone, HCFA and death certificate controls would have been helpful. What counties were included? What was the rural/urban makeup of the 13 counties? Were Seattle and Tacoma included? How were the controls "group matched" to the cases? Did over-matching or inappropriate urban/rural matching occur? Is it surprising that 58.5% of the study population had exposure to chlorophenols (Table 3)?

2. Adequacy of Exposure Information from Self-Reports

   The authors did not discuss adequacy of information recalled as far back as 40 years. Nor did they discuss the adequacy of exposure information from next-of-kin (needed for 1/3 of the study population). In our experience, next-of-kin are not very reliable regarding details of occupational exposure. It would have been helpful to have description of percent response for the various types of questions, and a discussion of the confidence the authors have in the responses.

3. Adequacy of Exposure Assessment

   More detail is needed to understand the data and the criteria used by the consultants to determine the categories of low, medium, and high occupational exposure.

4. Analysis

   The data presented on Tables 3, 4, 5, and 7 are difficult to interpret for several reasons:

   a. It is not clear which the categories are mutually exclusive (E.g., Table 4 categories sum to 79.9% of population, but Table 3 indicates that only 36.7% were exposed to phenoxy herbicides.).

   b. Some categories seem to be missing from the tables (E.g., Table 5 lists 47.9% of population with potential exposure to chlorophenols, but Table 3 indicates that 58.5% were exposed.).

c. The actual numbers of STS and NHL cases in each category are not presented.

d. It would have been useful if the authors had constructed and utilized in analysis a single measure reflecting both the duration and the intensity of exposure for each individual.d.

e. The authors deal with "chlorophenols" only superficially. The "chlorophenols" are not defined. It is possible that the exposure is to pentachlorophenol in these individuals, although the authors refer only to 2,4,5-trichlorophenol in the Introduction. Since dioxin contaminants differ in these two chlorophenols, it would be helpful to know the criteria used in the assessment of exposure. It is unclear how the overall OR for STS in chlorophenol exposed individuals is 0.99 (CI = 0.7-1.5) on page 904, but 7 or 10 occupational categories in Table 5 have OR greater than 1.

5. Conclusions

a. The authors found that overall, for the whole group, there was no increased risk for STS or NHL among those reporting any exposure to phenoxy herbicides or chlorophenols. However, for several subgroups, statistically significant risks were observed, and for many subgroups elevated but not statistically significant risks were found. Since many categories included small numbers of people, it is possible that low power accounts for the lack of statistical significance, and it is possible that the statistically significant positive results are due to chance. The authors do not discuss these points.

b. The authors state on page 902 of the current report that the elevated risk in farmers of 1.33, CI = 1.03-1.7, is consistent with reports from other studies which have identified farmers at increased NHL risk. However, the results from questions specifically inquiring about phenoxy herbicide usage appear to contradict the conclusions drawn by Hoar et al. that phenoxy herbicides, especially 2,4-D, are associated with increased risk of NHL in Kansas (Hoar, SE et al. "Agricultural herbicide use and risk of lymphoma and soft tissue sarcoma" JAMA, 1986 256:1141-1147). The authors do not address this point.

Comments on "Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to Phenoxyherbicide and Chlorinated Phenol Exposure in Western Washington"

JNCI 1987;78:899-910
Han K. Kang, Dr. P.H.
Veterans Administration

1. Study Design

This was a population based case control study in 13 counties of Western Washington State to evaluate the relationship between occupational exposure to phenoxyherbicides and chlorinated phenols and soft tissue sarcoma (STS) and non Hodgkin's lymphoma (NHL). A total of 128 STS cases and 576 NHL cases, aged between 20 and 79 at diagnosis during the years 1981-84 and 694 controls; group matched to NHL cases by vital status and 5-year age group were included in the analysis. All study subjects were male. Information on occupational exposures to herbicides, chlorophenols and other chemicals, and subjects' residential, military and medical histories was obtained through an in person interview lasting approximately one hour.

The Mantel-Haenszel-method was used to calculate estimates of relative risks as odds ratio and the method of Miettinen was employed to calculate 95% confidence intervals. In addition, logistic regression analysis was made to evaluate the joint effects.

2. Conclusions

The authors concluded that no significantly elevated risk of STS was seen among those exposed to phenoxyherbicides, chlorophenols, or among individuals involved in activities or occupations which had the potential for exposure to these chemicals. However, they stated, "the present investigation demonstrate increased risks of NHL in several specific occupations in which phenoxyacetic acid herbicides are used, as well as for prolonged occupational exposure to these substances".

3. Critique

This study appears to be appropriately designed and carefully executed and followed customary precautions to minimize bias leading to spurious association. Data analysis seems appropriate and conclusions are supported by the data presented. I nonetheless have the following observations to make:

a. Controls were group matched to NHL cases, not to STS cases. As a result there was significant difference in the distribution of ages between STS cases and controls: 28% of the STS cases fell within the 20-39 age category whereas 10% of the controls fitted in this age category. Intuitively, one can assume that individuals at younger ages would have less chance of exposure to these substances through their work or would have shorter work histories than individuals with 40+ years of work histories. It would have been helpful had the age distribution (Table 2) been presented in 5 year intervals rather than 20 year intervals.

b. Description of "proxies" are in order. Were they spouses, parents, siblings, friends, or other relatives? Quality of information may vary depending on the relationship of respondents to the subjects. Although quality control measures were described as "to verify the accuracy of the data collected by interview", it was in fact only for consistency of response, not for accuracy.

c. It was stated that "exposure" for all variables refers to that occurring prior to the date of diagnosis for the cases and prior to the date of interview for controls. Cases were diagnosed during the years 1981-84 and the interviews were conducted during the years 1983-85. This arrangement may have introduced small but systematic observation bias for underestimating the risk because controls were afforded a minimum of 1 year or maximum of 4 years of additional "exposure" period as compared to cases.

d. It was not clear whether control subjects were men without cancer or men without STS or NHL. The abstract describes controls as "controls without cancer" and in the text controls were described as "a control group without STS or NHL".

e. The authors recognized the importance of validating the diagnosis of STS. In fact they eliminated 33 individuals (21%) originally selected as STS cases from the study following pathologic review. According to Table 1, a total of 163 STS cases were interviewed of which 33 cases were eliminated as a result of the pathologic review. However, in the text I read only 155 cases were submitted for pathologic review. In other words it seems as though 8 STS cases were never subject to pathologic review, yet they were included in the study.

f. The authors described conducting the interview during a period (1983-85) of low local or national media attention to the herbicide and cancer issue as a deliberate measure taken to reduce the likelihood of recall bias. I found the statement somewhat presumptuous.

(1) I don't know about at a local level but certainly there was extensive media coverage at the national levels during the years 1983-85.

(2) Whether there was or was not wide spread media attention was immaterial. It seems to me that the authors had few options because this study did not begin until 1983.

4. I don't believe any of my comments will make significant differences in the final conclusions. The comments do, however, suggest a need for further clarifications in presentation and for paying more attention to details. In every other way, I think the study is a good one and supports a basis for concern that certain occupations involving potential exposure to phenoxyherbicides increase the risk of developing NHL.

HAN K. KANG, Dr. P.H.

Critique of "Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to Phenoxyherbicide and Chlorinated Phenol Exposure in Western Washington"

J.S. Woods, *et al*.

Study design and execution: This is a straight-forward, carefully done case-control study. All customary steps appear to have been done to assure data quality and to avoid bias. Definition of exposure (verification of exposure classification) is a bit soft, but they tried hard. This is a difficult arena. Analyses are appropriate.

Findings: No trend of increasing risk of STS or NHL was observed for exposure to either class of chemicals. Subgroup analyses for specific occupational groups also showed no excess risk for STS but did show increased risk for NHL among farmers and forestry herbicide sprayers. They postulated that there had to be exposure to the chemical of concern plus other unknown factors to produce the NHL. For those occupational groups exposed to chlorophenol there was no excess risk for NHL, but for lumber graders (a very small subgroup) there was a modest elevation in the OR ($p<.05$).

Other special analyses investigated the potentiating effects of immunosuppressive conditions and of differing hypothetical latent periods after exposure.

There is a long discussion of why these essentially negative results fail to support the positive findings from Sweden, focusing principally on shorter and more intensive exposure in Sweden vs. longer, more intermittent exposure yielding lower body burdens in Washington, but this is very conjectural. This study does not support the thesis that exposure to Agent Orange as it occurred in Vietnam is associated with NHL or STS.

Review of article for Science Panel, AOWC
Carl A. Keller, Ph.D., NIEHS

December 7, 1987

Title: Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma
in Relation to Phenoxyherbicide and Chlorinated
Phenol Exposure in Western Washington.

James S. Woods, et al., JNCI 78, 899-910, 1987

This all male study compares the occupational experience of 128 Soft Tissue Sarcoma (STS) and 576 Non-Hodgkins Lymphoma (NHL) cases and 694 controls in 13 counties of Western Washington State. Cases were diagnosed between 1981 and 1984 and were identified through a population based tumor registry and group matched by vital status and age to randomly selected controls from the same population. Study subjects were interviewed for life-time residential, military and medical histories and occupational exposures to herbicides, chlorophenols and other chemicals. The STS cases were reviewed for accurracy of diagnoses, and the study seems to have been conducted using standard epidemiological principles for case-control studies.

It is not clear how individuals' exposures were identified. The authors state that the coding of occupational exposures was based on job descriptions, but elsewhere it is stated that information derived from questionaire data was used to determine exposure to specific chemicals. The results in table 3 indicate that there were no statistically significantly elevated odds-ratios for either STS or NHL at any estimated intensity of past occupational exposure to phenoxyherbicides or chlorophenols. On the other hand, table 4 indicates that farmers and forest herbicide sprayers have been at higher risk of NHL than unexposed persons, and that these occupations present a medium to high potential for exposure to phenoxyherbicides. Also, table 5 indicates that lumber graders have had an elevated risk for STS and had high potential for exposure to chlorophenol. The exposure classification may not be comparable among these three tables. If table 3 represents a more precise and individualized estimate of specific chemical exposure, then it can be concluded that occupational exposure to phenoxyherbicides or chlorophenols did not increase the risk for STS or NHL in this population.

Specific occupational groups which did show an elevated risk for one of these sarcomas may have been the result of chance among the many confidence intervals which were calculated-- at least one of them was very small in that only 1 % of study subjects were involved. That the large group of farmers had an elevated risk for NHL is not consistant with the recently reported Kansas study by Hoar et al., and farmers are likely to have had a large number of possible exposures other than phenoxyherbicides. Results of the present study include significantly elevated risks for NHL which were associated with exposure to several industrial chemicals involving a sizable proportion of the population.

The only result in this study which is suggestive of a causal association is the statistically significantly elevated odds ratio of NHL for those with 15 years exposure to phenoxyherbicides more than 15 years before diagnosis. Unfortunately, the authors did not include any details of how this was measured nor how many persons or what kinds of occupations were involved. The authors did use logistic regression to estimate interaction between various study factors, but apparently did not utilize multivariate analysis to estimate the relative contribution of several factors simultaneously. It may have been more useful to compare the relative importance of occupational category, duration

DEPARTMENT OF THE AIR FORCE
USAF SCHOOL OF AEROSPACE MEDICINE (AFSC)
BROOKS AIR FORCE BASE, TEXAS 78235-5301

1 DEC 1987

REPLY TO ATTN OF: EK

SUBJECT: Review of "Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to Phenoxyherbicide and Chlorinated Phenol Exposure in Western Washington," (Woods, JS, et al. JNCI, Vol 78, No. 5, May 1987), HHS Memo, 25 Nov 87

TO: Dr John F. Young
Director, Division of Reproductive and
Developmental Toxicology
NCTR
Jefferson AR 72079

1. This study appeared to have been well planned, conducted, interpreted and written. The authors properly tested the equivalence of the living and deceased groups before pooling the data for analysis.

2. They used excellent techniques to assess and monitor the quality control of their questionnaire and pathological data collection methods.

3. The data concerning other risk factors which is presented in Table 6 is very valuable and they should be commended for providing it. These data will be useful in other studies.

4. The discussion section was excellent. Care was exercised in interpreting the data and weaknesses of study design were recognized and fully discussed. The approach to the differences in this study and the Swedish studies of Hardell was interesting.

5. Suggestions for clarification:

a. Were patients with unconfirmed or missing pathological specimens included in the data base?

b. If there was a 21% error rate in the diagnosis of Soft Tissue Sarcoma, could not a similar error be present in the diagnosis of Chloracne? Without verification of this difficult diagnosis, any association of chloracne with phenoxyherbicides is questionable.

c. The differences between the analyses of dose response (nonsignificant) and the occupation-specific groupings (significant in some instances) could easily have been due to inaccuracies in the exposure indices.

6. Overall, this study makes a significant contribution to the scientific literature on the possible effects of phenoxy herbicides. It does not have a direct effect on the issue of exposure of Vietnam veterans, but does provide useful information on the general issue of the health effects following the use of agricultural/industrial chemicals.

William H Wolfe
WILLIAM H. WOLFE, Colonel, USAF, MC
Chief, Epidemiology Division

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Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, DC 20510-8025

JOHN H. GIBBONS
DIRECTOR

November 19, 1987

The Honorable G.V. Montgomery
Chairman
Committee on Veterans' Affairs
U. S. House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

I am writing in response to the letter from you and your colleagues concerning the State of Washington study of soft-tissue sarcomas and non-Hodgkin's lymphomas in relation to various chemical exposures. I have asked staff members in the OTA Health Program to review the study and provide written comments. By the end of November, they will have completed their review, which I will send to you and your co-signers.

If you have any questions or comments on the study before that time, please do not hesitate to call me, or Clyde Behney or Hellen Gelband in the OTA Health Program (8-6590). Thank you for your continued interest and support.

Sincerely,

Jack Gibbons

John H. Gibbons

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Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, DC 20510-8025

JOHN H. GIBBONS
DIRECTOR

FEB 11 [illegible]

February 4, 1988

The Honorable G.V. Montgomery
Chairman
Committee on Veterans' Affairs
U. S. House of Representatives
Washington, D.C. 20515

Dear Sonny:

Enclosed is an Staff Paper, prepared by the OTA Health Program, reviewing the paper, "Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to Phenoxyherbicide and Chlorinated Phenol Exposure in Western Washington" (Journal of the National Cancer Institute 78(5):899-910, 1987), in response to the request of you and your colleagues in your joint letter of October 16, 1987.

The study examined the occurrence of two types of cancer, soft tissue sarcoma (STS) and non-Hodgkin's lymphoma (NHL) in men in relation to various occupational chemical exposures and other factors thought to be associated with these cancers. The study was well designed and the analyses appear to be appropriate. The key analyses concern two classes of chemicals, chlorophenols and phenoxyherbicides, which were heavily used in western Washington State, the study area. The major limitation of the study, as has been the case with many studies of herbicide and chemical exposure, was the lack of a quantitative measure of human exposure. Exposures were categorized based on job descriptions and expert judgment.

As you stated in your letter, the investigators found no association of either STS or NHL with their best estimates of aggregate exposure to either class of chemical, even in the "high intensity" categories. There were three findings of modestly increased risk, however, associated with particular jobs or activities undertaken sometime during the lives of the men in the study. These include: 1) NHL among farmers; 2) NHL among those who reported spraying forests with herbicides; and 3) STS among those who worked as lumber graders. While the chemical exposures in the first two cases may have been predominantly to phenoxyherbicides, and in the third, chlorophenols, the particular exposures or other risk factors that might be related to the excess risk are unknown.

This study does not provide support for a hypothesized connection between Agent Orange and subsequent development of STS and provides very limited support for a connection with NHL.

The study did find factors other than chemical exposures associated with NHL, and the findings are consistent with those of many previous studies: those findings are conditions (either disease related or the result of medical treatment for serious disease) of impaired immunologic function. If evidence of an increased NHL risk, as was suggested by the recent VA mortality study, is corroborated by the CDC NHL case control study, these might provide clues for exploring potential NHL risks other than exposure to Agent Orange.

I hope you find this helpful. If you have any further questions about it, please do not hesitate to call me or Hellen Gelband, of the OTA Health Program (at 8-6590), who was responsible for the review.

Sincerely,

Jack

John H. Gibbons

enclosure

OTA Critique of:

"Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to
Phenoxyherbicide and Chlorinated Phenol Exposure in Western Washington"
by James S. Woods, Lincoln Polissar, Richard K. Severson,
Linda S. Heuser, and Bruce G. Kulander
(Journal of the National Cancer Institute 78(5):899-910, 1987)

Study Description

The purpose of the Woods et al. study was to investigate possible associations between the development of either soft tissue sarcoma (STS) or non-Hodgkin's lymphoma (NHL) and known or inferred (on the basis of occupation) exposure to two classes of chemicals, chlorophenols and phenoxyherbicides. All men, aged 20 to 79 at diagnosis of STS or NHL, who were reported to a registry covering western Washington State during the period 1981 through 1984, constituted the pool of cases for the study. Controls for live men in the case group were selected from the general population of men in the same geographic area (by a combination of methods), in the same age frequency distribution as the NHL cases. Controls for those men in the case group who had died before the study began consisted of men who had died of causes other than cancer (excluding also homicide and suicide) during the study period (identified through death certificates) and were within the age range of the case group when they died.

Initially, 206 (150 living and 56 dead) men with STS and 746 (527 living and 219 dead) with NHL were identified from the registry as meeting study criteria. Controls, chosen in a ratio of 1.2 per NHL case, initially numbered 910. Excluding those whose physicians (of men in the case groups) refused to allow the patients to be interviewed or instances in which the individuals themselves declined to be interviewed, and those who were later found to have been misdiagnosed or were ineligible for other reasons, the final totals were:

OFFICE OF TECHNOLOGY ASSESSMENT CRITIQUE OF THE PAPER:

"Soft Tissue Sarcoma and Non-Hodgkin's Lymphoma in Relation to Phenoxyherbicide and Chlorinated Phenol Exposure in Western Washington"

by James S. Woods, Lincoln Polissar, Richard K. Severson,
Linda S. Heuser, and Bruce G. Kulander
(Journal of the National Cancer Institute 78(5):899-910, 1987)

Staff Paper

Prepared by Hellen Gelband

Special Projects Office of the Health Program

Office of Technology Assessment
U.S. Congress

February 1988

The views expressed in this Staff Memorandum do not necessarily represent the views of the Technology Assessment Board or its individuals members.

128 STS (97 living, 31 dead), 576 NHL (402 alive, 174 dead), and 694 controls (475 living, 219 dead). Each participant (or a proxy) was interviewed to find out about past exposures to chlorophenols and phenoxyherbicides, job descriptions, military histories, and information about potential risk factors for NHL and STS, such as immunosuppressive disorders or use of immunosuppressant medication (in the case of NHL).

Each job title (e.g., farmer) and specific activity (e.g., spraying herbicide from a backpack sprayer) was given a relative "rating" for potential exposure to each category of chemical (chlorophenols and phenoxyherbicides). These ratings, combined in various ways, were used in the analyses.

Findings

Overall, about 40 percent of the study population had some exposure to phenoxyherbicides, and about 60 percent to chlorophenols. The main aggregate analyses broke the potential exposure experiences for each category of chemical into categories of high, medium, low, and none. In those analyses, no significantly elevated risks (odds ratios) were found for either STS or NHL.

The investigators also looked for associations between particular occupations and activities involving potential exposure to the two classes of chemicals and the occurrence of STS or NHL. Out of a relatively large number of such analyses, three emerged as elevated at levels of statistical significance suggesting that they are not very likely to be due to the play of chance, though no finding is so strong as to exclude the possibility that it might be explained by chance alone. The three findings are:

1. An elevated risk of NHL among farmers, in whom the probable exposure is to phenoxyherbicides, the estimate suggesting that among farmers the risk of developing NHL is 1.33 times the risk

for non-farmers. There were a relatively large number of farmers in the study population (about 30 percent), so this estimate fits within a fairly narrow range (1.03 to 1.7) of variation (95 percent confidence limits) within which the actual odds ratio would fall.

2. An elevated risk of NHL among those who reported spraying forests with herbicides (potential exposure to phenoxyherbicides) at some time, the estimate suggesting a risk 4.8 times that of individuals not reporting forest herbicide spraying. Only 1 percent of the study population fell into this category, therefore the range of variation (95 percent confidence limits) about the 4.8 estimate is rather wide (1.2 to 19.4).

3. An elevated risk of STS among those who worked as lumber graders, the potential exposure being to chlorophenols, suggesting that the risk of developing STS is 2.66 times that for individuals not reporting that occupation. A relatively small number, 3.1 percent of the study population, reported some experience as lumber graders, and the 95 percent confidence limits about the estimate range from 1.1 to 6.4.

Elevated risks of NHL were also found in association with medical conditions suggesting compromise of immune function, and with certain occupational exposures other than chlorophenols and phenoxyherbicides (DDT, organic solvents, lead and lead arsenate, and welding fumes). No other factors were found in association with STS. No analysis of military experience was included in this paper. According to the primary author, few in the study population were Vietnam veterans, but information about that aspect of the study and other analyses not included in this paper will be presented in a future publication.

Significance of the Findings

As has been the case with most studies relating phenoxyherbicide exposure to health effects, the exposure information is not quantifiable, and must be assessed on the basis of subjective judgments. While these judgments appear to have been carried out according to a well-designed scheme in this study, it is impossible to know how well the categories correspond with actual exposures.

The strongest finding, when viewed in the context of other studies and the data presented in this study, is the modestly increased risk of NHL among farmers. The 1986 National Cancer Institute study of STS and NHL in Kansas found a similar increased risk. The increase is modest, however, and could be due to any number of factors associated with farming. In addition, though the authors downplay this, it is possible that "recall bias"--heightened or distorted memory of exposures among cancer patients when compared to people without cancer--may have also affected the findings, tending toward finding a risk where none might exist. The lack of association overall of NHL with what were considered high levels of potential exposure leaves considerable doubt that chlorophenols or phenoxyherbicides alone were responsible for the excess.

The risks identified, while not unimportant, do not represent large excesses of STS or NHL, and do not match what was seen in the earlier studies of Swedish forestry workers. This study does not provide support for a hypothesized connection of Agent Orange with subsequent development of STS and provides very limited support for a connection with NHL.

The study did find factors other than chemical exposures associated with NHL, and the findings are consistent with those of many previous studies: these findings are conditions (either disease related or the result of medical treatment for serious disease) of impaired immunologic function. If evidence of an increased NHL risk, as was suggested by the recent VA mortality study, is corroborated by the CDC NHL case control study, these might provide clues for exploring potential NHL risks other than exposure to Agent Orange.

VETERANS' ADMINISTRATION VETERANS' ADVISORY COMMITTEE ON ENVIRONMENTAL HAZARDS

SCIENTIFIC REVIEWS OF "SOFT TISSUE SARCOMA AND NON-HODGKIN'S LYMPHOMA IN RELATION TO PHENOXYHERBICIDE AND CHLORINATED PHENOL EXPOSURE IN WESTERN WASHINGTON" BY JAMES S. WOODS, LINCOLN POLISSAR, RICHARD K. SEVERSON, LINDA S. HEUSER, AND BRUCE G. KULANDER.

MINUTES OF THE VA ADVISORY COMMITTEE ON ENVIRONMENTAL HAZARDS

April 27-28, 1987

The Deputy Administrator of Veterans' Affairs, the Chief Medical Director, the Chief Benefits Director, and the General Counsel made brief, introductory remarks.

Mr. Meadows noted that there was a lay vacancy on the Committee and requested that Committee members forward the names of individuals for consideration by the Administrator for appointment to the Committee.

Dr. Kurland noted the large number of materials being submitted for review by the Committee and commented that because it was important that the Committee not miss any significant development, it may be necessary for the Committee to review more papers than it would prefer.

Dr. Sinclair, as chairman of the radiation subpanel of the Scientific Council, then began a discussion of the radiation related studies.

Revisions in the Dosimetry of the A-Bomb Survivors

Dr. Sinclair reported on a recent meeting sponsored by the National Council on Radiation Protection on the new dosimetry at Hiroshima and Nagasaki. He stated that there were several important items in the dosimetry reassessement. First, the yield of the Nagasaki weapon changed from 22 kilotons to 21 and the Hiroshima weapon changed from 12.5 kilotons to 15 kilotons. Second, recalculations were done on the source terms (i.e., spectra of the radiations issuing from the weapons) taking into account the structure and the materials of the weapons. A major difference was reported for the Hiroshima weapon, principally in the neutron spectrum issuing from the weapon. This, together with new transport calculations resulted in differences in both the neutron and gamma dosimetry for Hiroshima. Third, changes were noted in the calculations of shielding and in organ doses. Fourth, the changes in the dosimetry impacted on the risk estimates. The effect of the dosimetry is not large, ranging from no change to an increase of up to a factor of two, depending on the organ considered and the RBE assigned to the neutrons. In addition to the dosimetry changes, the risk estimates were also affected by the additional data that had been acquired since the 1980 BEIR report and the 1977 UNSCEAR report were prepared. These led to further increases. In response to a question about the implications of these changes for the occupation forces of Hiroshima or Nagasaki, Dr. Sinclair noted that the risk estimates would be higher but given the low doses they received, it would not change the overall appraisal of their risk.

Review of Radiation Papers

The first paper reviewed by the Council was "Multiple Myeloma Among A-Bomb Survivors," by Ichimaru, et al. (JNCI 69: 323-328 (1982).) The principal reviewer for this paper was Dr. Upton and the secondary reviewer was Dr. Webster. The authors reviewed the mortality of survivors of the atomic bomb explosions dying with multiple myeloma. The study subjects were drawn from the life-span study sample for Hiroshima and Nagasaki consisting of a total study population of nearly 100,000 people. The follow-up years were 1950 to 1976. There were 29 cases of multiple myeloma; 14 cases were observed in the controls whereas 16 were expected. Ten cases were observed among the survivors having 1 to 49 rads to the bone marrow versus 11 cases expected. Those having doses in excess of 50 rads were observed to have 5 cases of multiple myeloma whereas 1.8 cases were expected, a significant excess. The excess cases were also confined largely to the group that was exposed in the 40 to 59 age bracket. No excess was observed in the over 60 or under 20 years age groups. Also, the excess cases were found among those having the largest doses (in excess of 50 rads). It was further noted that that the excess did not appear until later (more than 20) years. The authors concluded that their analysis showed that the standardized relative risk adjusted for city, sex, and age at the time of the bombings increased with absorbed radiation dose to the bone marrow. The increased relative risk, the authors noted, did not appear to differ between cities or sexes and was demonstrable only for those survivors whose age at the time of the bombings was between 20 and 59 years. The estimated risk for those individuals was approximately 0.48 cases per million person years per rad for bone marrow total dose. The excess risk did not become apparent in individuals receiving 50 rads or more in marrow total dose until 20 years or more after exposure.

Dr. Upton noted that the earlier literature generally did not conclusively relate the induction of multiple myeloma to radiation exposure but that more recent data from Japan does show an apparent excess of multiple myeloma among the heavily irradiated survivors.

Dr. Webster concurred with Dr. Upton's assessment. He emphasized the points that the multiple myeloma appeared to have a long latency period and that there was no significant excess among those in the study who had less than 50 rads exposure.

3.

The Council members believed the study to be applicable to the veterans' experience and that the conclusions reported were supported by the data. It was the consensus of the Council that the latency period of five years for multiple myeloma currently found in the guidelines was unreasonably short, that a more reasonable minimum latency period would be 15 years. There was also concern that the excess was found only in those having exposures higher than 50 rads. One of the criticisms expressed about the paper was the failure of the authors to look more closely at the below 50 rads exposure group. The consensus of the Council was that while there was an association of multiple myeloma with high (in excess of 50 rads) exposure, the Council could not rule out the possibility of an association at lower levels.

The next paper reviewed was "The Plutonium Controversy" by John Gofman, M.D. (JAMA 236: 284-286 (1976)). Dr. Bender served as the principal reviewer. It was the author's contention that plutonium's carcinogenicity had been seriously underestimated and that reliance upon a plutonium energy economy would result in an excess of 130,000 additional fatalities per year in the United States. Council members questioned the paper's conclusions and noted that the author in every choice he made took the higher figure with a resultant multiplicative effect. The consensus was that the paper may be somewhat pertinent to the veterans' experience but that the conclusions expressed were not supported by the data and that the VA's guidelines should not be changed on the basis of this paper.

The Council next reviewed a paper by Christoffel and Swartzman, "Nuclear Weapons Testing Fallout: Proving Causation." (AJPH 76: 290-292 (1987).) The principal reviewer was Dr. Upton. This paper described the events leading to litigation by residents of areas downwind of the atomic weapons test sites against the United States government and discussed the court's handling of that litigation. One of the significant aspects of the case reported on (Allen v. United States, 588 F. Supp. 247 (D. Utah 1984)) was the shifting of the burden of proof; once the plaintiff had demonstrated the existence of substantial, appropriate, persuasive and connecting factors between defendant's negligent creation of a radiological hazard and plaintiffs' subsequent development of a biological condition consistent with that exposure, the burden shifted to the defendants to disprove a relationship. It was noted that the case, which several plaintiffs had won at trial, was reversed on appeal. The appellate court had held that the doctrine of sovereign immunity prevented the United States from being held liable.

4.

The next paper reviewed was by Darby, "Some Recent Statistical Analyses of Two Long-Term Studies of Exposure to Ionizing Radiation." (Stats. in Med. 5: 539--546 (1986).) Dr. Webster and Dr. Upton served as the principal and secondary reviewers. The author looked at two major studies and determined areas where the results were in agreement or reinforced each other. The two studies were the life-span study of the survivors of the Hiroshima and Nagasaki bombings and a study of a group of patients who had been treated with x-rays for ankylosing spondylitis. First, she looked at the question of relative risk for leukemia and other kinds of malignant disease and she found a substantial constancy of the relative risk, with two exceptions: leukemia and central nervous system tumors. She also found substantial agreement in the risk per rad for leukemia in the two studies of approximately two cases per million per year per rad. She also noted a parallelism between the two studies for the adult age groups in the relative risk for leukemia and solid cancers. The relative risk for solid cancers in both studies looked ostensibly constant as a function of progressing time. The conclusion reached by the author was that statistically the relative risk model appears to be the most consistent with the data. She further concluded, "the similarity of the findings in two high dose studies, where exposure took place under very different conditions, increases confidence in generalizing from these studies to other irradiated populations and detailed modeling of the radiogenic risk indicates a simple relative risk model for a particular group of cancers."

In his assessment of this paper, Dr. Webster noted that there were relatively wide error bars in the data but that these were not shown in the paper. Dr. Sinclair noted that this paper presented strong evidence in support of the relative risk model and that the absolute risk model is incompatible with the data. Dr. Sinclair also noted that this kind of study can only deal with all solid tumors as a group. The Council believed that while the analysis was relevant in terms of risk analysis it did not assist in answering the issue of the probability of developing a radiogenic cancer.

The Council then reviewed an editorial entitled, "Dermatologic Radiotherapy, the Risk-Benefit Ratio." (Arch. Dermatol. 122: 1385-1388 (1986).) Dr. Sinclair, the principal reviewer, noted that the editorial was occasioned by a paper on the side effects of radiotherapy. That paper reported on the results of a study of 14,140 patients in Sweden who had received grenz ray for superficial skin cancers, mostly on the lower legs, with doses of 18 to 60 gray (1 gray equals 100 rads); eight of the patients subsequently developed squamous cell cancer. In 481 patients treated with more than 100 gray, no cancer developed. The editorial concluded, as did the study, that the risk of grenz ray therapy was small.

The editorial then went on to discuss the non-stochastic and other effects of radiation exposure, noted the risks and benefits of radiation therapy, and generally favorably commented upon it.

Dr. Webster felt that it should be noted that the study which prompted the editorial involved non-penetrating, superficial exposure to grenz rays.

Mr. Conway stated that the editorial was selected for discussion because of its description of the risks associated with radiation exposure. The Council's discussion focused on the absence of skin cancer as among those considered in the editorial to be radiogenic. There was a general consensus that skin cancers could be considered to be radiogenic following exposure to 100 rads or more. Dr. Upton noted that recent work at the National Institutes of Health may shed more light on the risks of skin cancer following exposure to lower levels of ionizing radiation. It was recommended that this study be reviewed by the Council and Dr. Upton agreed to furnish a reference to it.

Another editorial entitled, "Human Effects Following Exposure to Ionizing Radiation," (Arch. Dermatol. 122: 1380-1382 (1986)) was next discussed with Dr. Bender serving as the principal reviewer. This editorial was occasioned by a presentation that had been made by two Russian physicians on the Chernobyl nuclear accident. Essentially, the editorial noted the increase in malignancies in the Hiroshima-Nagasaki population and the threat of radiation exposure to overall human health.

The Council characterized this editorial as being factually erroneous, uninformed and not of any significance.

The next paper discussed was Evans et al., "The Influence of Diagnostic Radiography on the Incidence of Breast Cancer and Leukemia." (N. Eng. J. Med. 315: 810-815 (1986).) Dr. Upton served as the reviewer for this paper. The study sought to estimate the numbers of excess cases of leukemia and breast cancer attributable to diagnostic radiography. The conclusion of the authors was that there was a small effect of radiation-induced carcinogenisis in relation to tumors of the bone marrow and breast. Induced cases of leukemia were estimated to be 1% of all cases of leukemia and somewhat less than 1% for induced cases of breast cancer.

Accompanying the report were several letters to the editor which noted that some of the age-specific coefficients used to predict radiation-induced breast cancer were outdated. The Council agreed with this assessment.

The Council next considered a paper by Linos, et al., "Low Dose Radiation and Leukemia" (N. Eng. J. Med. 302: 1101-1105 (1980).) Dr. Sinclair served as the principal reviewer and Dr. Bender was the secondary reviewer. This was a case control study on 138 patients with leukemia and the exposures they had received from diagnostic x-rays with matched controls. The authors concluded that there was no statistically significant increase in the risk of developing leukemia after radiation doses of 0 to 300 rads (3 gy) to the bone marrow when the amounts were administered in small doses over long periods of time.

A series of letters to the editor followed this study. (N. Eng. J. Med. 303: 814-816 (1980).) The principal criticism expressed was that the analyses were based on a small number of cases and that the authors had mixed together types of leukemia known to be induced by exposure to ionizing radiation with those that are not. The Council in its analysis agreed with the criticism that the study was of too low power for the study's negative findings to be conclusive.

The Council next addressed an article by Nussbaum entitled, "Survivor Studies and Radiation Standards." (Bulletin of the Atomic Scientists 41: 62 (Aug. 1985).) Dr. Webster, the principal reviewer, noted that the principal thesis of the article was that cancer risks from low-level radiation exposure are significantly higher than would be expected on the basis of internationally accepted standards for radiation protection. The author questioned the reliance upon the atomic bomb survivor data noting that the data collection did not begin until 1950. He noted that during the interval between 1945 and 1950, the survivors had experienced harsh weather conditions and inadequate food and medical supplies and poor sanitation services. He suggested, therefore, that those surviving until 1950 experienced the equivalent of the healthy worker or "survivor" effect with the result that the death rate among these individuals should have been significantly lower than the national average for Japan. Since it was not, the author questioned the conclusion that the only correlation with exposure was increased mortality due to cancer. The author also criticized other studies and put forth several studies which are contended to be supportive of the author's thesis that radiation is far more dangerous than officially acknowledged.

The Council faulted the author for failing to note the existence of a number of studies and reviews which refute or question the papers the author relied on. Consequently, the Council did not believe the paper to be credible.

Following this, there was a general discussion concerning whether the Council should review editorials, commentaries, or studies not appearing in peer-reviewed journals. It was noted that adherence to such a policy would eliminate a great deal of dioxin-related materials from consideration by the Council. It was further argued that review of such materials by the Council would assure the veteran community that a given study or paper had undergone a form of peer review by the Council's review process. Accordingly, the Council agreed it to be appropriate to continue to review materials without regard to whether it appeared in a peer-reviewed journal.

Next, the Council reviewed a paper by Zufan and Luxin entitled, "An Epidemiological Investigation of Mutational Disease in the High Background Radiation Area of Yangjiang, China." (*J. Radiat. Res.* 27: 141-150 (1986).) Dr. Bender and Dr. Webster served as the principal and secondary reviewers. This paper concerns an epidemiological study investigating whether or not there is a higher rate of mutation-based disease (cancer, hereditary disease, and congenital defects) in inhabitants exposed to high levels of background radiation versus those who were exposed to normal levels of background radiation in a control area. The annual individual external exposure to environmental gamma radiation was 330 millirad per year in the high backround radiation area and 114 millirad per year in the control area. The interim conclusions reported by the authors were: (1) no statistically significant differences were noted for total nor site specific cancer mortality rates between the two areas; (2) the rates of hereditary disease and congenital defects was almost identical in the two areas; and (3) a higher frequency of Down Syndrome was noted in the high background area which may be due to the age of the mothers at the time of birth as well as the age distribution of the children examined. The authors did note that further studies were needed before conclusions could be arrived at.

8.

The Council had difficulty assessing this paper because of the incomplete presentation of the data. In the course of discussing the paper, Dr. Bender provided a brief description of the differences between stable and unstable chromosone aberration and how their appearance is sensitive to radiation exposure.

Selected Questions on Radiation Topics

1. The Council next addressed the question of whether male breast cancer should be considered radiogenic. Dr. Webster led off the discussion with a summary review of the literature. He noted that male breast cancer is a relatively rare disease, having an incidence rate of less than 1 in a 100,000. A number of single case reports were described in which breast cancer developed following therapeutic exposure of the male. There seemed to be parallels with female breast cancer which is generally accepted as radiogenic. Dr. Upton questioned whether the hormonal differences between men and women may play a role as a promoting influence or as a cofactor for the development of breast cancer in women following radiation exposure. Concern was expressed that given the normal, low incidence rate of breast cancer among men, it may not be possible to conduct a scientific study to conclusively answer the question. The current state of the scientific literature is that there is no evidence that male breast cancer is not radiogenic and a number of anectdotal reports that it is. A recommendation was made that the word "female" be deleted from the VA's current guidelines. A further recommendation was made that the weak nature of the positive association and the absence of negative evidence be noted. The Council agreed and adopted the recommendation.

2. The Council next addressed the question of what constitutes a "high" level exposure and "low" level exposure to ionizing radiation. Dr. Upton noted that it depends on the reason for asking the question. If you are concerned with radiation protection, you may give a different answer than if you are trying to determine a causal association. The members of the Council agreed and noted that, in many respects, the selection of a figure was somewhat arbitrary. Mr. Conway explained that the question was raised because oftentimes reference would be made to a given cancer being shown to be radiogenic at a "high" dose but not at a "low" dose with no definition being given for "high" or "low."

Dr. Bender proposed that virtually everyone would agree that a dose below 10 rads would be considered "low" and a dose above 100 rads as "high." There was general concern that the expression of the Council's answer to this question include a number of caveats; for example, the rate of exposure, the age at the time of exposure, and the organ exposed were all important considerations. Also the Council believed that the statement should reflect the differences between stochastic and non stochastic effects.

3. The Council next addressed the question of the appropriate latency period for posterior subcapsular cataracts and non malignant thyroid nodular disease. Dr. Upton reported on a paper by George Merriam in which it appeared that the latent period between exposure and the subsequent appearance of cataracts is an inverse function of the dose, i.e., the greater the dose, the shorter the latency period with the time of onset ranging from 6 months to many years. The Council also discussed the minimum dose that could result in the development of opacities of the lens and agreed that for there to be a causal association, the radiation dose would have to be at least 200 rads. Concerning the non malignant thyroid nodular disease, the Council advised that that is a stochastic effect, having no threshold dose, with a minimum latency period of 5 years.

4. A question was presented whether it was necessary for the Defense Nuclear-Agency to reconstruct an internal beta dose for a veteran claimant where the sole issue is the radiogenicity of the veteran's skin cancer. The Council advised such a reconstruction was not necessary. However, the Council did recommend that if external beta doses were not being calculated that they be calculated. The Council further noted that while an internal dose would not affect the development of a skin cancer, a complete exposure history, both internal and external, is preferred.

The Council did express concern about the absence of mention of other risk factors that may be responsible for the development of skin cancer, such as exposure to ultraviolet radiation and the type of skin cancer involved.

The Council also discussed various aspects of the radiogenicity of skin cancer. The discussion prompted the suggestion that the Council consider whether or not skin cancer has a threshold dose and, if so, what that dose is. Dr. Upton agreed to address that issue.

10.

Review of Agent Orange/Dioxin Related Papers

The Committee next turned its attention to Agent Orange related studies. Dr. Yanders and Dr. Colton provided a brief overview of the 1986 mortality update of the "Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides" (the Ranch Hand study). This report (by Wolfe et al.) is part of a 20 year epidemiological investigation and is the fourth mortality analysis conducted. Like the preceding three, this report also found no demonstrable health effects which could be conclusively attributed to herbicide or dioxin exposure. The Council believed the study to be applicable to the veterans' experience and that the guidelines should not be changed in light of this study.

Dr. Lathrop next reviewed the article by Wayne Hall, "The Agent Orange Controversy After the Evatt Royal Commission," (Med. J. of Australia 145:219-225 (1986)). The author noted the findings of the Royal Commission that Australian veterans were not exposed to toxic levels of chemicals in Vietnam; that they were not at any increased risk of fathering children with birth defects, or contracting cancer; and that although they had slightly higher rates of psychiatric disorders, heart disease, alcoholism, and alcohol-related disease, these effects were determined to be unconnected with exposure to chemicals in Vietnam. The author urged that these findings and the bases for them be given the widest possible publicity to dissolve the misapprehension that Vietnam veterans have been poisoned by herbicides. The Council noted this article but offered no substantive comments on it.

The next article discussed was "Health Needs of the Vietnam Veteran Exposed to Agent Orange." (West and Leon, Nurse Practitioner 11: 38-40 (1986).) Dr. Lathrop served as the principal reviewer. The article related or referred to a number of animal studies and some studies of the health effects of exposure of humans to dioxin. The paper's authors urged that the nurse practitioner become knowledgeable about the signs and symptoms of toxic chemical exposure and the sources of support and aid for veterans within the community and familiarity with the results of Agent Orange related studies. The Council believed that this article was not based upon good science and that, therefore, it presented no basis for recommending any changes in the VA's guidelines.

11.

The Council next reviewed a study by Patterson, et al., "2,3,7,8-Tetrachlorodibenzo-p-dioxin Levels in Adipose Tissue of Exposed and Control Persons in Missouri." (JAMA 256: 2683-2686 (1986).) Dr. Yanders served as the principal reviewer. In this study, 2,3,7,8-TCDD levels were measured in adipose tissue samples taken from 39 persons with a history or residential, recreational, or occupational exposure and a control group of 59 individuals. The authors found that all persons in both the exposed and the control groups had detectable levels of TCDD in their adipose tissue but the exposed group had significantly higher levels. The Council believed that this methodologic study should be useful for future studies regarding the assessment of dioxin exposure. Dr. Lathrop noted that a similar analysis was being done of 250 Ranch Hand personnel and that preliminary results indicated levels significantly higher than those found in the study just reviewed. He also reported that comparison of recent blood samples with those taken several years earlier would permit the calculation of the half-life of dioxin to be done with greater precision.

The Council and the Committee then adjourned for the day.

Tuesday, April 28, 1987

Mr. Conway distributed a revised agenda, a copy of an April 27, 1987, Washington Post editorial on the Agent Orange litigation, and a copy of H.R. 1811, a radiation compensation bill. He noted that a hearing would be held on the bill on May 20, and that any comments the Committee may wish to make would need to be submitted to him by May 10, in order to have a statement by the hearing date.

Selected Radiation Questions

The Council then took up the proposed responses to the radiation-related questions the Council addressed yesterday. Following discussion, the Council agreed on the following statement concerning the radiogenicity of male breast cancer.

> The evidence for associating male breast cancer with radiation exposure is anecdotal and may never be conclusive given the rarity of the disease. Also, the nature of the positive evidence for an association between exposure to ionizing radiation and the subsequent development of male breast is weak and the negative evidence is non-existent. In view of these circumstances, it is recommended that the word "female" be deleted from the wording of the regulation so as to make "breast cancer" a radiogenic disease without regard to sex.

Concerning the minimum latency periods and exposure levels for posterior subcapsular cataracts and for non-malignant thyroid nodular disease, the Council agreed upon the following statements:

> The latency period for posterior subcapsular cataracts is six months or more following exposure to 200 rads or more.
>
> The latency period for non malignant thyroid nodular disease is five years or more following exposure.

13.

The Council then agreed to the following response to the Defense Nuclear Agency's inquiry concerning the necessity for calculating internal beta dose in a claim for benefits based upon skin cancer:

> The Council agrees that an internal beta dose need not be reconstructed in a claim soley for skin cancer. While an internal dose would not affect the risk of development of a skin cancer, a complete exposure history, both internal and external, is preferred.
>
> The Council expresses concern about the absence of reference to the reconstruction of an external beta dose in the question posed by the Defense Nuclear Agency. If external beta doses are not being calculated, the Council recommends that they be calculated.
>
> The Council also expresses concern about the absence or mention of other risk factors that may be responsible for the development of skin cancer, such as exposure to ultraviolet radiation and the type of cancer involved.

Review of Radiation Papers

The Council then reviewed the study by Johnson, "Cancer Incidence in an Area of Radioactive Fallout Downwind From the Nevada Test Site." (JAMA 251:230-236 (1984).) This study looked at Mormon populations in southwestern Utah exposed to radioactive fallout from atmospheric nuclear testing or from venting of underground nuclear detonations. The control population was the Mormon population for all of Utah. In looking at cancer incidence, the author found 109 more cases of cancer than expected, with leukemia being the most prominent early (1958 through 1966). The excess of leukemia persisted into the later period examined (1972 through 1980). Also observed were excess cases of lymphoma, thyroid cancer, breast cancer, gastrointestinal tract cancers, melanoma, bone cancer and brain tumors.

Dr. Webster, the principal reviewer, noted that the paper did not present complete references to the sources upon which a number of statements in the paper were based. Also, there was no organized data in the paper regarding integrated exposure in residential communities in southwest Utah which might relate to personal doses actually received. He also commented on the potential unreliability of the data collection and on the fact that the reported cancer cases were not verified by checking with the Utah Cancer Registry or with physicians, hospitals or the State Registrar of Vital Statistics. The excess solid cancers, therefor, may be exaggerated or even grossly wrong.

Dr. Lathrop observed that on the surface, this appears to be a reasonable epidemiologic effort but on closer examination of the methodology employed, he concluded that the paper was totally inadequate. He also noted that the cases had not been verified and that the opportunity for media bias resulting in an overreporting or exaggeration of reports of disease was very high and not addressed in the paper. Another serious shortcoming of the study was the use of a nonrandom selection method for the individuals selected for interview and the towns selected for examination.

Dr. Colton had difficulty understanding the study design. While the study was ostensibly a cohort study, the method by which the high-risk population was defined and selected was difficult to understand given the poor description by the author.

It was the consensus of the Council that the study was seriously flawed by methodological problems and that the VA's guidelines should not be changed in light of the study's findings.

The next paper discussed was "Cancer Mortality and Radioactive Fallout in Southwestern Utah," by Machado, Land, and McKay. (Amer J. of Epidemiology 125:44-61 (1987).) Dr. Upton served as the principal reviewer and Dr. Sinclair was the secondary reviewer. This study looked at three counties in the southwestern part of Utah, in which fallout levels were recorded to be higher, on the average, than elsewhere. (0.01-2.7 rad to organs such as red bone marrow, breast, and lung). The authors found no evident site-specific excess of any forms of cancer except leukemia. Mortality from all cancer sites combined was significantly lower in southwestern Utah than in the remainder of the state. Also there were no significant changes between the pre - and post - fallout periods in comparisons of mortality in southwestern Utah with the rest of the state or with the United States. The study did find a significant excess of childhood leukemia. The authors did not see this excess as conclusive but rather as hypothesis generating.

The Council considered this to be a very good study. More work perhaps should have been done to determine whether the leukemia and mortality incidence was real. In general, however, the Council believed this to have been a well-designed and well-conducted study.

The Council next reviewed a letter to the editor by Dr. Johnson (JAMA 125:166-168 (1987)) in which he discussed the Machado et al. study and compared it to his own. Dr. Johnson made three main points in his letter. First, he questioned why the authors who found an excess of leukemia did not also find an excess in solid tumors. Second, he gave a number of reasons why comparing incidence with mortality studies was not valid. Third, he contended that the exposure experience was greater than the official Department of Energy estimates. The Council was not persuaded by Dr. Johnson's letter.

Radiation Compensation Bills

The Council next took up consideration of H.R. 1811, a radiation compensation bill which would presume service connection for all forms of leukemia (except chronic lymphatic leukemia), for polycythemia vera, thyroid cancer, bronchogenic carcinoma, and female breast cancer becoming manifest to a degree of ten percent at any time within thirty years of the veteran's participation in an atmospheric atomic test or with the occupation forces. Mr. Conway briefly explained how presumptive service connection is applied by the Department of Veterans Benefits. Among the concerns raised by various members was the failure to consider the dose received when making a presumptive determination, the reinsertion of polycythemia vera as a radiogenic disease, the failure to take into account other sources of radiation exposure and other competing causes of cancer, the limitation of breast cancer in females as radiogenic, and the failure of this bill to take a scientific approach to the problem of compensation. Mr. Conway also briefly described a measure introduced by Senator Murkowski, S. 453, which would presume service connection for all forms of leukemia (except chronic lymphatic leukemia) becoming manifest within thirty years and liver cancer, multiple myeloma, or cancer of the bone marrow becoming manifest five or more years after the veteran's service with the occupation forces or participation in an atmospheric detonation of a nuclear device.

The Council then briefly discussed these measures. Dr. Lathrop moved that the Council formalize its views on these measures and the motion was seconded and carried.

16.

Review of Agent Orange/Dioxin Related Papers

Dr. Lathrop next led off the discussion of Agent Orange related materials. The first item was Chapter 11 of the "Health Assessment Document for Polychlorinated Debenzo-p-Dioxins," published by the Environmental Protection Agency (1985). Dr. Lathrop questioned what appeared to him to be an underrepresentation of veterans studies even given the fact that it was published in 1985. Dr. Lathrop focused on those pages discussing the Ranch Hand Study. He noted that the EPA questioned the kind of herbicide exposure the Ranch Handers had stating they may not have been as heavily exposed as ground troops. Dr. Lathrop challenged this and offered his opinion that EPA misinterpreted the exposure scenario in Vietnam. In general, he believed the document's conclusions with respect to soft-tissue sarcomas or non-Hodgkins' lymphomas reflected the consensus at the time the document was prepared.

Dr. Colton expressed the view that this chapter had limited scientific value in light of the fast developing scientific literature on this topic.

The Council generally was somewhat critical of what they perceived was an almost advocacy tone to the writing style. During the discussion, Mr. Conway noted that it was presented to the Council for review because the Commonwealth of Massachusetts had suggested that particular chapter as a resource of information. Dr. Shepard provided a brief history of the overall Health Assessment document.

Dr. Kurland next led the discussion on a review of the study, "Agricultural Herbicide Use of Risk of Lymphoma and Soft-Tissue Sarcoma" (Hoar, et al., JAMA 256:1141-1147 (1986)) which the Council had reviewed at its last meeting of the Committee. A paper, by Dr. Brian MacMahon, Professor and Chairman of the Department of Epidemiology of the Harvard School of Public Health, reviewed the scientific literature concerning the risk of lymphoma for agricultural workers exposed to 2,4-D. Dr. MacMahon concluded that the Hoar study was a well designed and well conducted one and that if no other evidence were available, it would provide a good basis for the hypothesis that agricultural exposure to phenoxyacetic acids, principally 2,4-D, increases the risk of non-Hodgkin's lymphoma. Dr. MacMahon also briefly looked at other related studies and then offered his conclusion that the weight of the evidence does not support the conclusion that there is an association between exposure to 2, 4-D and non-Hodgkins' lymphoma. Dr. Kurland agreed with Dr. MacMahon's analysis and with his conclusion that the final decision on the association awaits further studies.

Dr. Colton expressed the opinion that this critique was consistent with that expressed by the Council at its last meeting. Dr. Colton also pointed out the Council has the responsibility of assessing the cumulative weight of the evidence as well as looking at individual studies.

During discussion of this paper, it was pointed out that these studies focused on 2, 4-D which was not contaminated with dioxin. It was further observed that the mounting evidence suggested a need to pay attention to the various components of Agent Orange and not to focus soley on 2, 3, 7, 8-TCDD.

The Council next reviewed the paper by Kang, et al., "Soft-Tissue Sarcomas and Military Service in Vietnam: A Case Comparison Group Analysis of Hospital Patients." (*J. Occup. Med.* 28:1215-1218 (1986).) This case comparison study looked at the VA's Patient Treatment File to identify all Vietnam era veterans whose conditions were diagnosed as soft tissue sarcomas from 1969 to 1983. There were 234 cases identified. The comparison group consisted of 13,496 patients systematically sampled from the same Vietnam era patient population from which the cases were drawn. Military service information was obtained and analyzed. The authors found no significant association of soft-tissue sarcomas and military service in Vietnam..

Dr. Colton observed that limitation of the study was its hospital basis which may allow for selection bias and the possibility that controls did not exclude conditions that may have an association with Vietnam service. He also noted the author's point that there may have been insufficient observation time since, for the cases 80% had occurred within 10 years since possible exposure in Vietnam, perhaps too short a latent period. Dr. Colton further observed that there was no assessment of possible Agent Orange exposure and that the dependent variable was military service in Vietnam. Dr. Kurland concurred with Dr. Colton's review.

The Council believed the study to be relevant to the veterans' experience, that the conclusions were supported by the data, and that the VA's guidelines did not need to be modified in light of the findings.

18.

The Council next reviewed a study by Woods, et al., "Soft-Tissue Sarcoma and Non-Hodgkins Lymphoma in Relation to Phenoxyherbicide and Chlorinated Phenol Exposure in Western Washington." (JNCI 78: 899-910 (1987).)

This was a population-based case control study in Western Washington of 128 cases of soft-tissue sarcomas, 576 cases of non-Hodgkins Lymphoma, and 694 controls without cancer. Outcome variables were occupational history by job categories and an assessment of past occupational exposures to phenoxyherbicides or chlorophenols. The authors found no increased risk of either soft-tissue sarcoma or non-Hodgkins lymphoma associated with occupational history of exposure either to phenoxy herbicides or chlorophenols. With regards to occupational history by job category, however, there was found an increased risk of non-Hodgkins lymphoma for farmers, forestry herbicide applicators, and for those potentially exposed to phenoxy herbicides in any occupation for 15 years or more during the period prior to 15 years before cancer diagnosis.

Dr. Colton, the principal reviewer, described the study as being well-designed and well executed. The strengths of the study include its population basis, the careful choice of controls, the validation of the diagnosis of a soft-tissue sarcoma, the absence of any particular media attention during the period of data collection, and the validation by other sources the subjects' reported occupational histories and exposures to herbicides. The study's authors also presented various possible explanations for the discrepancies between their study's findings and other more recent U.S. findings with the Swedish studies of Hardell.

Dr. Lathrop expressed several concerns. First, he noted that when the overall population is looked at, no differences are found and that an association is seen only when the groups are further broken down. Secondly, he was concerned about the relatively low number of study subjects noting that with just a few misclassifications, the significance line can change quite easily. Overall, he believed the study to be extremely well conducted but noted that multiple comparison issue needs to be considered.

Dr. Kurland stated that he recalled a considerable amount of publicity regarding the use of herbicides by the Forestry Service and wondered whether there was, in fact, publicity to which the subjects were exposed and of which the investigators were unaware.

Dr. Colton expressed the belief that this study adds to the accumulating evidence of no relationship with herbicides exposure and the occurrence of soft-tissue sarcoma. With regards to the question of non-Hodgkin's lymphoma. Dr. Colton stated that this study raised the response to the question whether the VA's guidelines should be modified from a "no" to a "maybe." Dr. Lathrop noted the association of phenoxy herbicide exposure with non-Hodgkin's lymphoma warranted careful watching for new evidence.

The next study reviewed by the Council was by Boyle, et al., "Post Service Mortality Among Vietnam Veterans," (JAMA 257:790-795 (1987)) with Doctors Colton and Lathrop serving as the reviewers. This study examined the mortality experience through December 1983 of a group of approximately 9000 men who served in the army in Vietnam compared with a control group of about 9000 Vietnam era army veterans who did not serve in Vietnam. Over the entire follow-Up period, total mortality in Vietnam veterans was 17% higher than for other veterans. The excess mortality occurred mainly in the five years after separation from military service and involved motor vehicle accidents, suicide, homicide, and accidental poisonings. Thereafter, the mortality among Vietnam veterans was similar to that of other Vietnam era veterans except for drug-related deaths which continued to be elevated. Vietnam veterans had substantially lower mortality rates from diseases of the circulatory system. The authors noted that the excess in postservice mortality due to external causes among Vietnam veterans was similar to that found among men returning from combat areas after World War II and the Korean War.

The Council found that study to be well designed and well conducted. It noted that this study was a Vietnam experience study and consequently could shed no light on the issue of the efforts of exposure to Agent Orange.

Following this study, the Council addressed the question whether it should review Vietnam experience type studies contrasted with studies focusing on herbicide exposure, especially given the Council's charge in Pub. L. 98-542. Dr. Lathrop observed that if Vietnam experience studies that are well conducted and sufficiently large show no association of particular cancers that are of interest, then subcategorization of those results in other studies of Vietnam veterans would have considerably less meaning even if they are positive. It was the consensus of the Council that Vietnam experience studies would be reviewed by the Council but to the extent possible, the Council's focus should be on herbicide exposure.

The Council then reviewed a paper by Hatch and Stein, "Agent Orange and Risks to Reproduction: The Limits of Epidemiology." (Teratogenesis, Carcinogenesis, and Mutagenesis 6"185-202 (1986).) Dr. Taylor was the principal reviewer. This paper reviewed the findings of the Australian birth defects study, the CDC birth defects study, and the Air Forces' study of reproductive morbidity in Ranch Handers, analyzed the strengths and weaknesses of these studies, commented on the consistency and coherence of the studies, and concluded that service in Vietnam did not, in and of itself raise the risk for fathering malformed offspring but that given the difficulties of defining and measuring exposure to Agent Orange, it was premature to venture conclusions abut the proposed association with birth defects. The Council noted that this paper was a review article which presented no new data nor offered any new insights.

The next paper considered by the Council was Pearn, "Herbicides and Congential Malformations: A Review for the Paediatrician." (Aust. Paediatr. J. 21:237:242 (1985).) This paper which was reviewed by Dr. Taylor also summarized the findings of other research with respect to the teratogenic effects of herbicide exposure and concluded that there has been no evidence to indicate that a human herbicide teratogenic syndrome exists. As with the previous paper, the Council noted the paper did not present any new data nor any new insights.

The Council next discussed a paper by Constable and Hatch, "Reproductive Effects of Herbicide Exposure in Vietnam: Recent Studies by the Vietnamese and Others." (Teratogenesis, Carcinogenesis, and Mutagenesis 5:231-250 (1985)) with Dr. Taylor serving as the lead reviewer. This paper reported on the findings of unpublished epidemiologic investigations carried out by Vietnamese researchers which were presented in January 1983, at an International Symposium on the long-term effects of phenoxy herbicides held in Ho Chi Minh City. The paper commented upon the possible bias in selection and/or reporting that may have affected the reported findings. Other problems identified included the definition of exposure, the sources of the data on reproductive outcomes, and the limited efforts made to consider the potentially confounding effect of extraneous variables. Nine studies were reported on with varying study groups and research designs.

Following the review, the Council discussed the necessity for having a reproductive biologist available either as a consultant or as a member to assist in reviewing and evaluating papers related to reproductive effects. It was noted that while such expertise may be helpful, it was not essential when the papers being reviewed were of the sort discussed here, principally review papers without any original or new data being presented. Should an original study dealing with reproductive effects be presented for discussion, the Council may wish to have the benefits of such expertise available to it.

Finally, the Council considered a paper by Webb, et al., "The Diagnosis of Dioxin-Associated Illness." (Am. J. Prv. Med. 2: 103-108 1986).) Dr. Taylor led the discussion of this paper which was essentially a review of the major health findings with an intention of establishing diagnostic criteria for dioxin toxicity. These included; chloracne, abnormal urinary excretion of uroporphyrins, liver function abnormalities, peripheral nueropathy, hypertriglyceridemia or hyperchlosterolemia and documentable evidence of profound weakness and depression. The Council again agreed that this paper presented no new data nor offered any new insights.

Veterans' Advisory Committee on the Health-Related Effects or Herbicide Exposure

The Committee then heard from Hugh Walkup, Ph.D., a member of the VA's Advisory Committee on Health-Related Effects of Herbicides. Dr. Walkup provided a brief overview of the activities of the Herbicide Committee and offered some observations concerning how the two committees might work together. First, he suggested the committees might address the standards to be applied in making decisions concerning establishing causality. Secondly, how should studies be selected for consideration and what factors are important in evaluating a study individually and in context with other studies. Finally, he suggested the committees might look at how to define their roles and how best to achieve their respective goals. Dr. Walkup then extended an invitation to the members to attend the meeting of the Herbicide Committee which was scheduled for the following day.

There then followed a general discussion with Dr. Walkup.

22.

Non-Hodgkin's Lymphoma and Phenoxy Herbicides

Dr. Colton then raised the issue of the association between non-Hodgkin's lymphoma and phenoxy herbicide exposure. Dr. Lathrop expressed the opinion, with which Dr. Yanders concurred, that the issue was approaching resolution, that another study or so may cause him to rethink the issue and perhaps make a recommendation to the Administrator. Among the reasons expressed for being reluctant at this point were the lack of a similar effect in non-agricultural groups, some methodological concerns with some of the studies showing an association, the approximate balance of positive and negative studies, and the ability to be able to design and conduct scientific studies that can fairly straight forwardly and quickly address the issue.

Statement on H.R. 1811

The Council then considered a proposed statement that could be used in the formulation of a Committee position on H.R. 1811. Among the items particularly commented upon were the concern that the bill was not based on scientific knowledge, that it failed to permit consideration of a number of highly relevant factors such the dose of radiation received, the smoking history, and the family history of the veteran, and the opportunities for other exposures. The Council and the full Committee approved, by voice vote, the proposed statement as amended.

The Committee tentatively set November 16 and 17, 1987, as the dates of the next meeting and subsequently adjourned.

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THE UNDER SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

OCT 9 1987

OCT 19 1987

The Honorable G.V. (Sonny) Montgomery
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. ~~Montgomery~~ Chairman:

This is in reply to your letter of September 6, 1987, requesting that the Science Panel of the Agent Orange Working Group, review and comment on the Veterans Administration study entitled, "Proportionate Mortality Study of Army and Marine Corps Veterans of the Vietnam War".

The Science Panel met on September 14, 1987, to review and comment on the study. I am appending the summary report from Dr. Ronald Hart, Director, National Center for Toxicological Research, who chairs the Science Panel, and in addition, the individual comments of key members of the Science Panel.

I believe the specific findings discussed in the report which warrant follow up investigation and analysis are clearly identified.

Should you have further questions, please do not hesitate to ask.

Sincerely,

Don Newman

Don M. Newman
Chair
Domestic Policy Council
Agent Orange Working Group

cc: Dr. Ralph Bledsoe, DPC
Dr. William Graham, OSTP
Mr. Gary Bauer, OPD

XEROX TELECOPIER 295 ; 9- 8-87; 8:30 AM;

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

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National Center
For Toxicological Research
Jefferson AR 72079

September 8, 1987

The Honorable Don R. Newman
Chairman, Domestic Policy Council
Agent Orange Working Group

Review of VA submission to JAMA
"Proportional Mortality Study of Army and Marine Corps Veterans
of the Vietnam War"
by P. Breslin, H.K. Kang, Y. Lee, V. Burt, and B.M. Shepard

Summary prepared by

Dr. Vernon Houk & Staff at CDC,
Dr. Donald Barnes & Staff at EPA,
Dr. Marilyn Fingerhut at NIOSH, and
Dr. Ronald W. Hart & Staff at NCTR

This proportionate mortality ratio (PMR) study appears to be well executed in mechanics. However, the presentation and discussion of the results do not provide the necessary caution in interpretation but do allow uninitiated to make causal inferances where they may not exist.

PMR studies are usually used to generate, not test hypotheses. The article appropriately recommends further work to evaluate causal factors.

This study can not be used to infer anything about Agent Orange or any other specific cause of effect other than being a Vietnam veteran.

The authors emphasize only the statistically significant positive findings. From this study the Marines have an increased risk due to Non-Hodgkins Lymphomas and lung cancer; however, the risk of death from genitourinary disease and all cancers combined is statistically significantly decreased.

No evaluation of latency is presented for lymphoma or lung outcomes. An evaluation of time-to-tumor data should be conducted.

The findings for lung cancer in Marine Vietnam veterans are provocative, although similar observations were not made in other studies of Vietnam veterans. The absence of smoking histories makes the interpretation of this finding difficult.

It is not surprising to encounter the small number of statistical departures from expected mortality seen in this study. Some of these could have arisen by chance alone. This study, as originally designed, cannot conclusively clarify mortality risks for Vietnam veterans, let alone elucidate possible causative factors within, or outside of, the Vietnam experience.

Ronald W. Hart, Ph.D.
Chairman, AOWG Science Panel

Summary of Review of VA submission to JAMA
"Proportional Mortality Study of Army and Marine Corps Veterans of the Vietnam War"
by P. Breslin, H.K. Kang, Y. Lee, V. Burt, and B.M. Shepard

Summary prepared by
J.F. Young, D.W. Gaylor, R.L. Kodell, and J. Chen
National Center for Toxicological Research
Jefferson, Arkansas 72079
September 8, 1987

- Regardless of any possible methodological flaws, this study can not be used to infer anything about Agent Orange or any other specific cause of effect other than being a Vietnam veteran.

- From the write up, one can not check the statistical procedures and therefore must assume that it was done correctly using acceptable methods; however, a more detailed description of the methods with references would be helpful.

- From this study the Marines have an increased risk due to Non-Hodgkins Lymphomas; however, the Army risk is lower than expected but not significantly. When combined, the overall risk is less than expected with a PMR ~ 0.95.

- The manuscript is for the most part written clearly; however, there are still obvious errors and statements made that are not well documented. Positive findings are pointed out but corresponding negative findings are not discussed.

- Statements are made on page 14 that PMR values may be inflated or deflated. Life-table analyses could be conducted to overcome these limitations.

- It is not clear how age and race adjustments were made in the analyses. Were the average age of the Vietnam and non-Vietnam groups the same?

#3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date · September 11, 1987

From Director
Center for Environmental Health and Injury Control

Subject Review of VA Mortality Study

To Ronald W. Hart, Ph.D.
Director
National Center for Toxicological Research

The Veterans Administration (VA) has conducted a proportionate mortality study (PMR) of 24,235 deaths among U.S. Army and U.S. Marine male veterans who served in Vietnam and 26,685 deaths among male veterans of the same two services who did not serve anywhere in Southeast Asia. All deaths were identified from the VA BIRLS file and occurred between July 4, 1965, and March 1, 1982. These deceased veterans had to have served in the military sometime between July 4, 1965, and March 1, 1973. Career and non-career, officers, and enlisted men, as well as reservists, were included. In-service deaths occurring before 1974 and men dying from war-related injuries were excluded. In service deaths after 1973 were included.

Within the group of Vietnam veterans, the fraction of all deaths attributable to a particular cause was computed and compared to the corresponding proportion for non-Vietnam veterans. The comparison was done using the proportionate mortality ratio (PMR) technique in which age at death, race, and branch of service were taken into account. There was no adjustment for calendar year of death or rank. Altogether, PMRs were computed for 18 major cause of death groupings and for 23 specific cancer sites.

We will address our concerns in data collection, data analysis, and interpretation.

Data Collection. Are the BIRLS tapes truly at least 94 percent complete? From the CDC Mortality Study which used multiple sources of mortality we found that BIRLS was less complete.

Data Analysis. Why do the authors emphasize only the statistically significant positive findings? Why were not the significant decreases in deaths from genitourinary diseases (Table 3) and the decrease in deaths from all cancers for one-tour of duty veterans (Table 5) not discussed?

The lack of association between service in Vietnam and suicide needs to be reevaluated in light of the CDC finding that they were increased only in the first 5 years after discharge. CDC used the time period since discharge rather than year of death. This subject was repeatedly brought

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up with the VA prior to completion of their analysis. The CDC study would indicate that grouping by 10 year periods would minimize the effect.

The findings for lung cancer and NHL in Marine Vietnam veterans are *provocative, although* similar observations were not made in other studies of Vietnam veterans. The absence of unusual mortality from soft-tissue cancers is consistent with some previous studies but at variance with others. Because so many statistical tests were done on the data set, these apparent findings could be due to chance. It would be helpful to see a more detailed analysis in which mortality from these cancer sites is examined by calendar year in Vietnam, rank, MOS, and principal duty. These additional analyses would help in deciding whether some factor related to the Vietnam experience is responsible for the apparent association.

Interpretation. The authors suggest that these were major differences in the findings of previous studies cited, but there are in fact few major differences in the findings.

Referenced studies were not critically discussed. There has never been, for example, an association demonstrated between lung cancer and phenoxy herbicides except in the Zack Study (Ref. 29) where 3.6 cases were expected and 6 were found in those exposed to 2,4,5-T. Those authors state that they cannot evaluate trends in lung cancer deaths as they relate to occupation because of "limitation in the data."

As noted above, it is not surprising to encounter the small number of statistical departures from expected mortality seen in this study. These could easily have arisen by chance alone. This study, as originally designed, cannot conclusively clarify mortality risks for Vietnam veterans, let alone elucidate possible causative factors within, or outside of, the Vietnam experience. Reasons include lack of a defined population-at-risk, incomplete ascertainment of deaths, and absence of "exposure" data on individual veterans.

This PMR study appears to be well executed in mechanics. However, the presentation and discussion of the results do not provide the necessary caution in interpretation and allow the uninitiated to make causal inferences where they do not exist.

Vernon N. Houk, M.D.
Assistant Surgeon General

Comments on "Proportionate Mortality Study of Army and
Marine Corp Veterans of the Vietnam War" by P. Breslin *et al*.
Marilyn Fingerhut
September 6, 1987

- Use of BIRLS for a PMR study is reasonable.

- Structure of PMR study is reasonable: Random sample of complete file of BIRLS, with Vietnam exposure confirmed; death certificates obtained (96.9% followup), adequate size (at least for Army).

- PMR studies are usually used to generate, not test hypotheses. The article appropriately recommends further work to evaluate etiological factors. The media reports have not conveyed this information.

- The problem at hand results from the timing of the release of the article, and the inclusion of a sentence in the Abstract (inappropriately) referring to Agent Orange exposure.

- The structure of the study is appropriate; the scientific weakness of the article lies in the analysis and interpretation of the results. The authors can revise the article for submission to a journal.

- The weakness of the article results from 1) the absence of data evaluating elevations in other smoking related diseases in the Marines, 2) absence of latency evaluations for the malignancy outcomes, 3) lack of data evaluating the adequacy of the marine comparison group, and 4) inadequate evaluation of the limitations of the PMR study design.

- No evaluation of latency is presented for lymphoma or lung outcomes. Service was '64-'73, deaths were '65-'82. The article does not evaluate the relationship of time of exposure to time of death.

- No data are provided to show whether other circulatory or respiratory deaths were elevated in army and marines for conditions associated with smoking.

- It is unclear whether the cancer outcomes were obtained in the overall PMR, or in a separate Proportionate Cancer Mortality Ratio (PCMR).

- The results for deaths from external causes and accidental poisonings are consistent with other studies of veterans and point out problems for veterans following this war.

- The nonVietnam comparison group for the Army is large, so the numbers can be expected to be stable; the same may not be true for the marines. It would have been helpful if, 1) the authors had carefully presented data to show that the marine Vietnam vs. nonVietnam populations were truly comparable, and 2) the authors had provided a table showing the expected numbers for each cause of death if the national population had been used as the comparison.

REVIEW OF VIETNAM VETERANS MORTALITY STUDY

A study of proportionate mortality among U.S. Army and Marine veterans who served between July 4, 1965 and March 1, 1973 and died before March 1, 1982 was reported by the Veterans Administration. The study included 19708 Army and 4527 Marine veterans who had served in Vietnam and 22904 Army and 3781 Marine veterans who had not served in Southeast Asia during tis period. The study included a random sample of about one-third of the potentially elligible veterans who had died during this period. The selection of study subjects and recovery of information on them appears to have been unbiased and appropriate.

The major findings from this study included a statistically significant excess of accidental and drug related deaths and paucity of suicides among Army veterans who had served in Vietnam compared to those who had not served in Southeast Asia. In addition, there was a statistically significant excess of lung cancer and non-Hodgkins lymphoma among Marine veterans who had served in Vietnam compared to those who had not. Several other findings were not mentioned in either the conclusions nor in the narrative, but are evident in the tables. These include a statisically significant decrease in mortality due to genitourinary diseases and cancer of the extra-cranial nervous system among Army Vietnam veterans. In addition, there appears to have been a signifcant decrease in cancer deaths among enlisted Army veterans with only one tour of duty in Vietnam, and among similar Marine veterans before 1975. There was also a significant increase in accidental poisonings among enlisted Marine Vietnam veterans dying before 1975.

The authors computed Standardized Proportionate Mortality Ratios (SPMR) and tested with the Chi-Square statistic (not presented in the tables). According to the reference used to justify this procedure (ref # 13), Professor Monson suggests using the Poisson approximation of the variance of the expected deaths, i.e., that the expected number of deaths approximates the variance. If this procedure is applied to the information which can be deduced from the observed number of deaths and the SPMR as given in the tables, several additional SPMRs appear to be statistically significant. These include an excess of all cancer deaths among Marine veterans who served in Vietnam, particularly single tour enlisted Marines after 1975. Other possibly significant findings would include a decrease in deaths due to infectious diseases and diseases of the blood, an increase in deaths due to musculoskeletal and connective tissue diseases, and a decrease in deaths from thyroid cancer and non-Hodgkins lymphoma among Army Vietnam veterans.

While there is no way to determine which statistical procedures are "correct", these results indicate that more significant findings are available in these data than have been dicussed in the manuscript. While this does not make it any easier to interpret the results, it does serve to point out the selective nature of the findings which have been emphasized in the manuscript. In particular, the inclusion of one-seventh of the abstract and considerable dicussion in the narrative to Agent Orange is misleading. Other possible explanations for the findings should receive relatively more emphasis.

Carl A Keller

Carl A. Keller, Ph.D.
Epidemiologist, NIEHS

9/8/87

COMMENTS ON "PROPORTIONATE MORTALITY STUDY OF ARMY AND MARINE CORPS VETERANS OF THE VIETNAM WAR"

Donald G. Barnes
U.S. Environmental Protection Agency

1. Proportionate mortality studies have inherent limitations which restrict their interpretation and conclusions; e.g., reduced PMR in one area necessitates increased PMR in another area. This particular study is a generally well-designed example of this type of investigation. The report clearly discusses the procedures, methods of analysis, and the conclusions, including caveats. The results should not be cited without an thorough appreciation of these caveats.

2. The study is a descriptive study which essentially suggests hypotheses for further investigation. As such, the study does not test any particular association, let alone prove any cause-effect relationship.

3. It should be noted that of all the PMRs the two identified as being of concern, while statistically significant, are modest (roughly 2) -- a tribute to the scale of the study.

4. Among the areas of concern is the question of whether there is an inherent difference between Marines in Vietnam, compared to non-Vietnam Marines and all Army troops. It has been suggested that the Marines in Vietnam had attitudes and behaviors (e.g., risk takers) which were distinguishable from other troops.

5. The diagnosis of Non-Hogkins lymphoma is not easy. There might be a bias in the recording of this diagnosis in cases in which it was known that the patient had served in Vietnam.

6. If one is concerned about the etiology of cancer vis a vis Vietnam, it would be preferable to exclude any cancers that appear prior to some minimal latency period; e.g., 10 years.

7. It would be enlightening to look at the proportionate cancer mortality ratios (PMCRs), which would examine the relative cancer experience in greater detail.

8. Possible followups include:
   a. An I Corps study of the Army veterans -- planned
   b. A periodic updating of the current study to take into account latency, etc. -- planned?
   c. A cohort study of the Marines
   d. A case-control study of the NHL and lung cancers in the Marines.

   The question of exposure still remains. Given the recent results of the CDC exposure validation study, it is not clear that options c and d are tenable.

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Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, DC 20510-8025

JOHN H. GIBBONS
DIRECTOR

October 23, 1987

The Honorable G. V. Montgomery
Chairman
Committee on Veterans' Affairs
United States House of Representatives
Washington, D.C. 20515

Dear Sonny:

As requested in the letter from you and Senator Cranston (September 8, 1987), we have reviewed the recent Veterans Administration "Proportionate mortality study of Army and Marine Corps veterans of the Vietnam war." The VA provided us a copy of the study and the New England Journal of Medicine reviewers' comments to the authors. The Journal did not accept the manuscript for publication after two rounds of review.

Overall, the methodology of this study appears sound and appropriate. The investigators achieved a remarkably high rate of ascertaining causes of death, finding such information for more than 98 percent of the 51,421 men eligible for the study. However, the report itself, as submitted for publication, would benefit from rewriting, both because what is presented could be greatly improved and because important information is omitted. The discussion on interpreting the results requires considerable attention. In addition, the failure to point out the causes of death that are underrepresented in the Vietnam veteran group leaves an unbalanced impression of the findings. Proportionate mortality studies have some built-in problems, and these ought to be brought out as well.

The major Journal reviewer criticism concerned the appropriateness of using deaths among non-Vietnam veterans as the comparison for Vietnam veteran deaths, in preference to U.S. male death patterns. We believe that the VA chose the appropriate control group. Because of the "healthy veteran effect," the U.S. male rate would make a poorer choice, except as a second line check on specific findings, which is an appropriate use. Our only suggestion regarding the control group is that VA consider using the combined Army and Marine non-Vietnam group as a comparison for the separate Army and Marine Vietnam veteran groups, simply to have a larger comparison population, with less random fluctuation in the numbers of deaths from individual causes.

The findings in Army veterans of more deaths than expected from "external causes" is consistent with findings from previous studies, including some state studies and the Vietnam Experience Study mortality analysis. The VA study, however, is much larger than any previous ones, and is a more reliable means of estimating the magnitude of the excess. Finding excesses of non-Hodgkin's lymphoma (NHL) and lung cancer among the Marines have generated the most heat from this study. We believe these findings should be taken seriously and that follow-up work be done to investigate possible explanations.

Cigarette smoking is the most obvious potential cause of the excess of lung cancer deaths. It is essential that smoking histories be obtained for these cases, and even more importantly, that information about smoking rates of Marines and other servicemen who did and did not serve in Vietnam be gathered. For the lung cancer deaths, it is likely that smoking history will appear on the hospital record. If not, next-of-kin could be contacted. These determinations should be made before any attempt is made to relate the lung cancer excess to other environmental exposures.

It has been suggested that the apparent excess of NHL might be a function of the small number of cases of this cancer overall. It is possible that the number in the non-Vietnam group is, because of random fluctuation and sampling variability, somewhat below what would, on average, be expected in that entire population, and that the number in the Vietnam group is at the high end. One of OTA's advisors compared the NHL finding with the expected proportion in the U.S. male population, however, and found the excess still be significant. We believe it should be followed up; while it may indeed turn out not to be a true excess, that conclusion cannot be made on present evidence. A first step in follow-up would be to retrieve medical records and histologic samples for all cases of NHL in both the Army and Marines. The pathology should then be reviewed blindly, perhaps by the Armed Forces Institute of Pathology. This should be done to determine whether the specific pathology--among the several types of NHL--can be identified, and to verify the accuracy of the diagnoses.

Determining possible causes of the NHL excess may be difficult, but preliminary investigation to identify factors that were different among Marines in and out of Vietnam, as well as possible differences between conditions in I Corps and the rest of Vietnam, would be valuable. In particular, the use of various medical drugs (e.g., anti-malarials) may have differed and could possible be related to the NHL finding. Because of the low likelihood of exposure as identified from military records, it appears unlikely that Agent Orange could be responsible for the excess.

CDC's Selected Cancers Study includes NHL. Even though that study is slated to continue through 1988, it might be possible to examine the NHL data now. Of the cancers in the study, more cases of NHL were expected than of any other type (three times the number of soft-tissue sarcomas), therefore there may well be a sufficient number of NHL cases already in the study for a reliable analysis. CDC should be urged to examine this possibility. If that study is or will be insufficient to answer this question, perhaps an additional case-control study should be considered, if there is a way to ensure enough Marine and I Corps veterans in the sample to investigate the specific hypothesis that risk is related to those characteristics.

One of the benefits of a proportionate mortality study such as the VA carried out is to generate hypotheses that can be further tested. It appears that this study has succeeded, and may be the key to some important information about the health of veterans.

I know that this study has occasioned resentment among some parts of the veteran community. The charge has generally been that the VA was withholding findings that might be of value to the veterans. These criticisms seem wholly unfounded. As we understand it, the VA began seeking publication of the report as soon as it was ready for submission. They have gone through the usual process of submission, review, revision, and resubmission. The paper is currently under consideration by the *Journal of Occupational Medicine*. Had the report been issued by VA before publication, they might rightly have been accused of releasing a paper that had not been through a peer review process.

The results of this study are important and should be presented fairly and fully. We urge VA to substantially redraft the paper and again pursue publication in a major medical journal.

I hope this discussion is of help to you. As always, if you have any further questions or comments, please do not hesitate to contact me or Hellen Gelband (who conducted the OTA review) or Clyde Behney, in the OTA Health Program (8-6590).

Sincerely,

Jack Gibbons

John H. Gibbons

Congreſs of the United States
Washington, D.C. 20510

September 9, 1987

Mr. Frederic Conway, III
Executive Secretary
Advisory Committee on Environmental Hazards
c/o Office of the General Counsel
Veterans' Administration
810 Vermont Avenue, N.W.
Washington, D.C. 20420

Dear Mr. Conway,

As you may know, the Veterans' Administration's Office of Environmental Epidemiology recently released the results of a study entitled "Proportionate Mortality Study of Army and Marine Corps Veterans of the Vietnam War".

The findings outlined in this report indicate that statistically significant excess deaths were observed among Army Vietnam veterans for motor vehicle accidents, non-motor vehicle accidents, and accidental poisonings and that Marine Corps Vietnam veterans appeared to have an increased mortality from lung cancer and non-Hodgkin's lymphoma.

As Chairmen of the Senate and House Veterans' Affairs Committees, we are writing to request that the Advisory Committee on Environmental Hazards review and provide comments on this report. We would also appreciate identification of any specific findings discussed in the report which warrant follow-up investigation or analysis. Due to the urgency of this issue, we ask that this review take place prior to the Advisory Committee's regularly scheduled meeting in November.

As always, we thank you for your continuing cooperation and assistance.

Cordially,

Alan Cranston
Alan Cranston
Chairman, Senate Committee on
Veterans' Affairs

Sonny Montgomery
G. V. (Sonny) Montgomery
Chairman, House Committee on
Veterans' Affairs

cc: Dr. John Gronvall

Office of General Counsel Washington D.C. 20420

Veterans
Administration

SEP 18 1987

Honorable G. V. (Sonny) Montgomery
Chairman, Committee on
Veterans' Affairs
House of Representatives
Washington, D.C. 20515

In Reply Refer To:

Dear Mr. Chairman:

This is in response to the letter you and Representative Montgomery sent requesting that the Veterans' Advisory Committee on Environmental Hazards review and comment upon the study entitled "Proportionate Mortality Study of Army and Marine Corps Veterans of the Vietnam War." That report has already been provided to the members of the Committee and will be discussed at the next meeting of the Committee which is now scheduled for October 15 and 16, 1987. It is fully anticipated that the comments and recommendations of the Committee will be forwarded to the Administrator of Veterans' Affairs during the following week. I will be happy to provide you with a copy of the Committee's assessment as soon as it becomes available.

Should you desire to have a member of the staff of the Committee attend the meeting of the Committee, it is expected that the mortality study will be discussed on Thursday, October 15, following the luncheon break. The Committee is currently scheduled to meet in Room 442, Lafayette Building, 811 Vermont Avenue, N.W. (across the street from Central Office).

Sincerely yours,

Frederic L Conway

FREDERIC L. CONWAY
Executive Secretary
Veterans' Advisory Committee
on Environmental Hazards

VETERANS' ADMINISTRATION VETERANS' ADVISORY COMMITTEE ON ENVIRONMENTAL HAZARDS

SCIENTIFIC REVIEWS OF VETERANS' ADMINISTRATION "PROPORTIONATE MORTALITY STUDY OF ARMY AND MARINE CORPS VETERANS OF THE VIETNAM WAR" BY P. BRESLIN, H.K. KANG, Y. LEE, Y BURT, AND B.M. SHEPARD.

October 16, 1987

Dr. Kurland noted that a draft statement concerning the proportional mortality study had been prepared and circulated to the members. He advised the members that the statement would be discussed later in the day.

Dr. Sinclair, as chair of the Radiation Panel, introduced Dr. Alvin Young of the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC). Dr. Young provided a brief overview of the involvment of CIRRPC in response to a request of the Veterans Administration concerning the applicability of the radioepidemiological tables to the VA's adjudication of claims for benefits based upon exposure to ionizing radiation. Dr. Mills then provided a more detailed description of the report prepared by the CIRRPC in response to the VA's request. He indicated that the report recommends the use of a screening dose to permit an initial screening of clearly nonmeritorious claims. He noted that the report covered eleven forms of cancer and not all of the cancers listed in the VA's guidelines as being radiogenic. He stated that the report did not deal with bone cancer, multiple myeloma, salivary glands, and skin cancers. He indicated that the recommended screening dose was a conservative one designed to exclude all true negatives. While this would result in some false positives surviving the initial screening, this would ensure that no true positive would be inappropriately eliminated.

Dr. Young and Dr. Mills then provided a brief description of the review process the document would be going through and indicated that the CIRRPC would be looking at the applicability of the tables to other Federal agencies.

Dr. Bender then provided a review of an article entitled, "Radioepidemiological Tables," appearing in the Journal of the American Medical Association. (Vol. 257, pp. 806-809 (1987).) The article noted a number of uncertainties in the tables and the criticisms that the tables have received. The authors of the article recommended that the tables, if they be used at all, be applied only under the conditions for which they were originally intended and not for estimating risk or probability of causation in medical situations involving diagnostic or therapeutic exposures of patients or occupational exposures of radiology personnel. Dr. Bender did not think that this article offered anything new nor was its recommendations germaine to any of the problems facing the VA.

Dr. Webster, the second commentator, concurred in Dr. Bender's statment. He did not beleive that the conclusions arrived at by the authors were supported by the arguments. Dr. Sinclair also agreed with this.

> development of lung cancer, it is critical that more analysis be done before drawing any conclusions about the relationship between service in Vietnam and later appearing lung cancer.
>
> Also, we take note of the blood serum assay study recently completed by the Centers for Disease Control wherein it was concluded that Vietnam veterans were not found to have significantly different levels of dioxin (2,3,7,8-TCDD) than non Vietnam veterans. This study raises a number of questions, not the least of which is whether studies of the effects of exposure to phenoxy herbicides are truly applicable to the Vietnam veterans' experience. That is, if, as the CDC study suggests, Vietnam veterans did not have significant exposures to the phenoxy herbicides 2,4-D and 2,4,5-T, components of Agent Orange, as determined by the absence of significant differences in levels of 2,3,7,8-TCDD, a contaminant of 2,4,5-T, between Vietnam veterans and non Vietnam veterans, then it may be inappropriate to consider studies of phenoxy herbicides' effects as being confirmatory of or contributory to the findings of this mortality study.
>
> We, therefore, recommend that the Veterans Administration not effect any changes in its current guidelines and that it diligently pursue additional research and analysis as expeditiously as possible.

After discussion, it was agreed that the Committee would make two consensus statements, one dealing with the mortality study findings and the other dealing with the CDC blood assay findings. Those statements read as follows:

> The Veterans Administration's "Proportionate Mortality Study of Army and Marine Corps Veterans of the Vietnam War" is a well-designed and well-conducted study. The general conclusion, no statistically significant differences in overall mortality between Vietnam and non Vietnam veterans, is supported by the reported data. Concern is raised by the statistically significant proportional mortality findings of excess non-Hodgkin's lymphoma and lung cancer among Marines who served in Vietnam. This finding did not appear among Army veterans who served in Vietnam during the same time period as the Marine veterans involved in the study. It is our best scientific and professional judgement that the findings concerning the

> non-Hodgkin's lymphoma and lung cancer, while statistically significant, should be interpreted with caution and are not conclusive.
>
> Reasons for this include the fact that a proportionate mortality study, by its very nature, cannot resolve by itself the question whether the observed results constitute a direct cause and effect relationship. A study such as this can only lead to the identification of issues requiring further study and analysis.
>
> In particular, with respect to the lung cancer finding, nothing is known about the smoking history of the study's subjects. Given the widely-accepted view of a causal relationship between smoking and the subsequent development of lung cancer, it is critical that more analysis be done before drawing any conclusions about the relationship between service in Vietnam and the subsequent occurrence of lung cancer.
>
> We, therefore, do not recommend that the Veterans Administration effect any changes in its current guidelines on the basis of this study.

The second statement pertaining to the blood serum assay study read as follows:

> We take note of the preliminary results of the blood serum assay study recently completed by the Centers for Disease Control. (Morbidity and Mortality Weekly Report 36: 470-475 (July 24, 1987)) The purpose of the study was to determine whether estimates of exposure based on military records or on interviews of U.S. Army veterans can identify those with heavy exposure to TCDD (2,3,7,8 tetrachloro-dibenzo-dioxin), a contaminant of 2,4,5-T, one of the components of Agent Orange. The study concluded, based upon recently drawn samples, that Vietnam veterans were not found to have significantly different levels of dioxin (2,3,7,8-TCDD) than non Vietnam veterans. This study raises a number of questions, not the the least of which is whether studies of the effects of exposure to phenoxy herbicides are truly applicable to the Vietnam veterans experience. The CDC study suggests that many U.S. Army Vietnam veterans may not have had appreciable exposures to the phenoxy herbicides 2,4-D and 2,4,5-T, components of Agent Orange, as determined by the absence of significant difference in levels of TCDD in serum lipids beteen Army Vietnam veterans and non Vietnam veterans. It may be inappropriate, therefore, to consider studies of phenoxy herbicides' effects as being relevant to the Vietnam experience.

15.

Mr. Conway advised the Committee of Dr. Taylor's resignation and requested that nominations be forwarded to him for consideration by the Administrator.

Whereupon, the Committee adjourned.

Frederic L Conway

FREDERIC L. CONWAY
Executive Secretary

APPROVED Oliver E Meadows
OLIVER MEADOWS
Chairman

February 18, 1988

Members in Attendance

Mr. Meadows
Colonel Bonner
Dr. Kurland
Dr. Sinclair
Dr. Colton
Dr. Yanders
Dr. Melvin
Dr. Webster (second day only)
Dr. Bender
Dr. Lathrop

Agency Officials in Attendance

Dr. Hobson
Dr. Kang
Mr. Drash
Mr. Thompson
Dr. Shepard
Mr. Day

Mr. Hickman
Mr. Drembus
Mr. White
Mr. Hippolit
Mr. Rosenblum
Ms. St. John

Office of the
Administrator
of Veterans Affairs

Washington DC 20420

Veterans
Administration

JUL 20 1988

Honorable G. V. (Sonny) Montgomery
Chairman, Committee on Veterans'
Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

Enclosed are responses to the questions raised by you and Congressman Hammerschmidt following the June 8, 1988, hearing on scientific research on the health of Vietnam veterans. Thank you for the opportunity to provide this additional information for the record.

Sincerely,

THOMAS K. TURNAGE
Administrator

Enclosure

cc: Honorable John Paul Hammerschmidt

"America is #1—Thanks to our Veterans"

CONGRESSMAN MONTGOMERY

Question: 1. When do you anticipate completion of the five follow-up studies to the Proportionate Mortality Study?

Answer: The "Military Medical Record Review," one of the five mortality study follow-up efforts was completed in February 1988. This study resulted in the finding that military medical records are not a reasonable source of information on cigarette smoking because veterans' smoking status was not routinely recorded in those records.

Anticipated completion dates for the other four mortality study-related efforts are as follows:

(a) Update of the Vietnam Veterans Mortality Study -- September 1988

(b) VA Patient Treatment File Review for Non-Hodgkin's Lymphoma (NHL) -- December 1988

(c) A Retrospective Study of Marine Corps Vietnam Veterans -- December 1990

(d) A Separate Mortality Analysis for Army Veterans Stationed in I Corps in Vietnam in Vietnam Veterans Mortality Study -- Projected completion by the U.S. Army Environmental Support Group of identification of unit locations in Vietnam (on or about the end of calendar year 1988)

Question: 2. How many veterans have sought health care under the provisions of Public Law 97-72 for conditions that may have been caused by exposure to dioxin or a toxic substance in a herbicide or defoliant used in Vietnam?

Answer: As of June 1988, it is estimated that there have been approximately 1.5 million outpatient visits and 26,000 inpatient admissions under the authority of Public Law 97-72.

Question: 3. Please describe the process followed by the VA to compile the review of literature on herbicides. For example, what criteria are used to select studies for inclusion?

Answer: The Veterans Administration has contracted with an independent contractor, via the competitive bid process, for the annual preparation of the "Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins." The report is prepared wholly and exclusively by the contractor through an independent assessment of the current state of science about the health effects of phenoxy herbicides, their contaminating polychlorinated dibenzo-p-dioxin impurities, and two other herbicides (picloram and cacodylic acid) used in Vietnam. The contractor identifies and reviews scientific papers that become available during each year.

In order to identify relevant literature, the contractor searches on-line data bases for literature published during the year. These searches cover the MEDLINE, TOXLINE, and CANCERLINE data bases of the MEDLARS on-line information system of the National Library of Medicine. Print-outs of these searches are manually screened to identify relevant resources not already included in the earlier reviews.

Searching of on-line data bases is of limited usefulness because of a lag time of approximately 6 months between publication of scientific reports and their entry into on-line data bases. Therefore, the contractor manually screens weekly issues of *Current Contents, Life Sciences* published by the Institute for Scientific Information, Philadelphia, Pennsylvania, and biweekly issues of *CA Selects: Carcinogens, Mutagens, and Teratogens* published by Chemical Abstracts Service, Columbus, Ohio. Approximately 20 scientific journals and current awareness publications available in the contractor's library are also screened.

Additional information is obtained at scientific meetings and at the regular meetings of the Veterans Administration Advisory Committee on Health-Related Effects of Herbicides. Also, in order to identify unpublished documents or documents published in unconventional resources, the contractors contact scientists who have been active in research on the health effects of phenoxy herbicides and dioxins.

Question: 4. Please describe the uses to which the VA's Agent Orange Registry has been put.

Answer: The Veterans Administration (VA), since the establishment in 1978 of the Agent Orange Registry (AOR) program of physical examinations of Vietnam veterans, has conducted a continuing review of the computerized data from those examinations. The review consists primarily of an analysis of the data to detect any significant health trends which might require more in-depth review. The data however, has limited scientific usefulness because it is derived from examinations of a self-selected population. Nevertheless, the VA will continue its review of this data base as an important feature of our overall efforts to resolve the health issues caused by Agent Orange.

Question: 5. What is the status of the VA's activities related to keeping Vietnam veterans informed about the link between their service and health? For example, when was the last Agent Orange update mailed out? What plans are there for bringing up to date the addresses of veterans on the Agent Orange Registry?

Answer: Since the Agent Orange Registry was initiated in 1978 over 236,000 concerned Vietnam veterans have participated in the examination process. Recent mailout efforts, including the mailout of the Agent Orange Review in March 1986 to registry participants, resulted in a significant number of mailouts being returned to the Veterans Administration (VA) as undeliverable because of address changes. No special effort is being undertaken or planned at this time to provide for an updating of addresses. To date, there is still no scientific or medical consensus that the possible exposure of Vietnam veterans to Agent Orange has had an adverse health effect on these individuals. Should future research results make it necessary to notify specific veterans or Vietnam veterans in general, the VA would consider updating the addresses utilizing the assistance of various resources including, but not limited to, internal VA listing, the U.S. Postal Service, Social Security Administration, various veterans service organizations and other sources. Efforts could also be made to request veterans' addresses, through the use of the media (i.e., television, radio, newspapers, etc). These extensive efforts would be undertaken only when there is a demonstrated scientific or medical basis for doing so. Under most circumstances an announcement of the research results and the suggested actions for the veterans to take would be made through the public media and should be more effective in reaching all the affected veterans.

Question: 6. What is the status of the Women's Agent Orange Study?

Answer: The Women's Health Study is designed to determine the impact of the total Vietnam experience on women who served in Vietnam. Among the issues to be addressed will be the reproductive experience of these women. The study cannot specifically address the issue of what, if any, effect exposure to Agent Orange may have had.

On July 1, 1987, a protocol to be used for the conduct of the Women's Health Study was provided to the VA's Office of Environmental Epidemiology by its contractor, the New England Research Institute. The protocol was transmitted on August 11, 1987, to the Office of Technology Assessment (OTA) for review and comment. The protocol was subsequently transmitted, for information purposes, to the Science Panel of the Domestic Policy Council Agent Orange Working Group (AOWG). On August 27, 1987, OTA's Advisory Panel conducted a formal review of the Women's Health Study protocol. The Director, OTA, in his letter of September 25, 1987, advised the VA of recommended revisions. The protocol was then resubmitted to the New England Research Institute for revision in accordance with OTA's recommendations. The revised protocol was returned to the VA on March 3, 1988. The VA's Research and Publications Committee conducted a review of the protocol and determined that it was unsatisfactory. The VA has requested its contractor to modify the protocol in accordance with recommendations of the Committee. The revision of the protocol will result in some delay in the actual conduct of the study. It is now anticipated that the conduct of the study will begin in January or February 1989.

CONGRESSMAN HAMMERSCHMIDT

Question:	1. Testimony to the Committee indicates that the VA Advisory Committee on Environmental Hazards has not been properly discharging its responsibilities. It is compared unfavorably to a somewhat similar advisory committee at the Environmental Protection Agency. Would you please comment on this?
Answer:	Criticism concerning the number of studies reviewed by the Veterans' Advisory Committee on Environmental Hazards and its Scientific Council prior to the time that it reviewed and commented upon the regulations proposed by the VA to implement Pub. L. No. 98-542 is premised, we believe, upon an incorrect assumption: that the Committee and its Scientific Council were required by the Act establishing them to review all pertinent scientific studies prior to the adoption of final regulations. Under the Act, the Committee performs several distinct functions: (1) the Committee reviews regulations based upon the knowledge and experience of the members: (2) the Committee recommends appropriate administrative and legislative action; and (3) the Council reviews and comments upon the emerging scientific studies that the Council deems to be relevant.

It should be remembered that Pub. L. No. 98-542 set forth very specific time periods within which the Agency had to promulgate final regulations. Within one hundred and eighty days of the date of the enactment of Pub. L. No. 98-542 (October 24, 1984), the Agency was required to have published proposed regulations and not later than one hundred and twenty days thereafter final regulations were to have been published.

The Committee held its first meeting in April 1985 (coincidentally, the same date as the publication of the notice of proposed rule-making). At its first meeting, the Advisory Committee received an orientation and overview of the issues of Agent Orange and ionizing radiation resulting from the detonation of a nuclear device. As soon as was feasible thereafter, the Committee held its second meeting for the purpose of reviewing the regulations as required by section 5(c)(1) of Pub. L. No. 98-542. To perform that function, the members of the Committee, who were selected for membership because of their professional expertise and knowledge, need only have brought to bear their knowledge and experience in providing advice on the proposed regulations. Under the Act, the Committee and its Scientific Council were not required nor expected to review all of the studies relevant to the issue of the health effects of exposure to Agent Orange or to ionizing radiation prior to the Agency's promulgation of regulations. Given the time available in which to review the regulations, the breadth of that task, and the busy schedules of the members of the Committee, it was not feasible for the Council to review more than the seven Agent Orange/dioxin related studies it did review prior to the time that the final regulations were required to be published. (It should be noted that the Committee has reviewed an additional fifty-six papers related to Agent Orange/dioxin exposure and a total of forty-eight papers relating to exposure to ionizing radiation.)

The process engaged in by the Environmental Protection Agency in developing its "Health Assessment Document for Polychlorinated Dibenzo-p-Dioxins" could not realistically have served as a model for the Veterans' Advisory Committee on Environmental Hazards. That was a multi-year effort and was not bound by strict statutory time periods within which the Agency had to act as was the case for the Veterans Administration and its advisory committee. Further, as noted, we do not believe that the Committee nor its Council was expected to undertake such an ambitious task as that taken by the Environmental Protection Agency.

With respect to the assertion that the Committee ought to review animal studies as did the Environmental Protection Agency when it undertook its review of the scientific literature, we continue to question the value of such an undertaking by the Committee. As a review of the EPA's "Health Assessment Document" shows, there is wide-spread species variability in terms of response to exposure to dioxin. The inconsistency of response makes the applicability of animal models to human experience questionable. Additionally, the method, type, duration and amount of exposure usually employed in animal studies do not mimic the exposure circumstances that often occur with humans.

One other fact needs to be kept in mind in weighing the validity of the actions of the respective agencies: the mission of the two agencies are very different and that impacts on the approach taken by the agencies in addressing a similar issue. The EPA has the responsibility of reducing, if not eliminating, the risk of harm to the environment and the consequential impact on human health attributable to chemical agents. That mission, of necessity, requires that a very conservative approach be taken so as to ensure that adverse risks are minimized. Reliance upon animal models for this purpose would be appropriate as we cannot predict with certainty which animal model is truly predictive of human response and which is not. The VA, on the other hand, has the responsibility of ensuring that veterans who suffer disability as a consequence of their military service receive the compensation to which they are legally entitled. This determination cannot be based upon speculation, however well-founded, but, rather, must be based upon "sound scientific and medical evidence" of a cause and effect relationship.

Question: 2. Why did the Journal of the American Medical Association decline to accept for publication the study mentioned on page 3 of your testimony?

Answer: The manuscript for the Proportionate Mortality Study of Army and Marine Corps Veterans of the Vietnam War was submitted for publication to the Journal of the American Medical Association (JAMA) on February 13, 1987. Following a period of peer review by reviewers chosen by JAMA the manuscript was returned to the VA for revision. On May 14, 1987, the manuscript was returned to JAMA in anticipation of its eventual publication. However, following this review of the revised manuscript, the VA was advised by the editor that a decision of non-acceptance for publication had been made. An explanation for the reasons underlying non-acceptance was never communicated to the VA.

Department of Medicine
and Surgery
Washington D.C. 20420

Veterans
Administration

JUL 27 1988

In Reply Refer To:

Honorable G.V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

Thank you for your letter of June 24, 1988, transmitting questions in reference to the June 8, 1988, hearing of your Subcommittee on Hospitals and Health Care.

If you have any questions regarding the response that I have enclosed, you may wish to contact me at the Center for Risk Management, Resources for the Future, 1616 P Street, N.W., Washington, D.C. 20036. My telephone number is (202) 328-5080.

Sincerely,

MICHAEL GOUGH, Ph.D.

Enclosure

"America is #1—Thanks to our Veterans"

1. Advisory committees such as the one you chair are composed of citizens with expertise and the willingness to use it for the country. What additional activities could be profitably undertaken by your Committee as we continue to grapple with the controversy surrounding Agent Orange?

The current scope of the Veterans Administration's Advisory Committee on Health-Related Effects of Herbicides is quite broad. The Committee has been reorganized during the last year, and I think that it is functioning effectively. The Committee itself is now deciding what activities should or could be undertaken. For instance, it will consider what kind of coordination might be of value to the various State Agent Orange committees. The Committee regularly attracts substantial audiences whose comments are carefully considered. The Agent Orange issue has also received the attention of several other VA advisory groups, including the Veterans' Advisory Committee on Environmental Hazards, Advisory Committee on Readjustment Problems of Vietnam Veterans, and Advisory Committee on Women Veterans. Any consideration of additional activities should consider the current activities of all the committees, and I expect that for the time being, anyhow, the committees themselves are well situated to plan and augment activities.

2. In your personal opinion, is the blood test as validated by CDC, a valid and accurate test for the levels of dioxin in humans?

All of the evidence available about correlations between blood levels of dioxin and adipose tissue levels of dioxin are consistent with the conclusion that the CDC "blood test" is a valid and accurate test for the levels of dioxin in humans. In my opinion, the world-wide acceptance of the blood test underlines the validity of the test.

3. In your personal opinion, is the approximate 7 year half-life of dioxin in humans a reliable number to use for purposes of retrospectively estimating exposure?

Yes. A great deal of information is available for the half-life of dioxin in the bodies of Ranch Hands a few years after exposure. The clear conclusion from those data is that the half-life is about 7 years. We have much less information about the kinetics of elimination right after exposure, say, within a few days or weeks. To my knowledge such measurements have been made in only a single man, and the half-life, based on measurements made over 69 days, was estimated at about 5 years (Poiger, H. and C. Schlatter, 1986, Chemosphere 15: 1489-1494). That estimate is in good agreement with the 7 years half-life measured in Ranch Hands. Furthermore, the animal studies that show that dioxin is eliminated at a constant rate are consistent with the idea that humans eliminate dioxin at a constant rate.

At the present time, I think that the evidence supports the idea of a 7-year half-life. Some people disagree, and I think that it is up to them to produce data to support their contentions rather than to second guess the 7-year half-life because of claims rather than data.

DEMOCRATS
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MACK FLEMING
CHIEF COUNSEL AND STAFF DIRECTOR

ONE HUNDREDTH CONGRESS

G.V. (SONNY) MONTGOMERY
CHAIRMAN

U.S. House of Representatives
COMMITTEE ON VETERANS' AFFAIRS
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JACK DAVIS, ILLINOIS

June 24, 1988

Maj. Gen. Alexander Sloan
Deputy Surgeon General
Department of the Air Force
Bolling Air Force Base
Washington, DC 20332-6188

Dear General Sloan:

In reference to our Subcommittee on Hospitals and Health Care hearing of June 8, 1988, I would appreciate it if you could answer the enclosed questions by July 20, 1988.

In an effort to reduce printing costs, the Committee on Veterans' Affairs, in cooperation with the Joint Committee on Printing, is implementing some formatting changes for materials for all full Committee and Subcommittee hearings. Therefore, it would be appreciated if you could provide your answers consecutively on legal size paper, single spaced.

Sincerely,

G. V. (SONNY) MONTGOMERY
Chairman

GVM:das

Enclosure

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FOR OPEN PUBLICATION

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DIRECTORATE FOR FREEDOM OF INFORMATION
AND SECURITY REVIEW (OASD–PA)
DEPARTMENT OF DEFENSE

Question 1: How were the Comparisons selected and matched?

Answer 1: The Air Force personnel assigned to Air Force units operating and maintaining C-130 aircraft in Southeast Asia from 1962-1971 were selected as the Comparison group for the Air Force Health Study (AFHS) because they comprised a reasonably large population of men who closely resembled the Ranch Hand personnel except that they did not work with, transport or spray the herbicides used in the Ranch-Hand mission. They were similar in military background, education, religious preference, general state of health, education and occupation. Both groups flew or maintained cargo aircraft operating in and around Vietnam. The specific individuals selected for the study were chosen in identical ways whether they were part of the Ranch Hand or Comparison cohorts. Records from the Air Force Military Personnel Center were reviewed to identify all individuals assigned to the Ranch Hand unit or to any of the C-130 units in Southeast Asia from 1962-1971. The individual personnel records of each of these people were carefully reviewed to verify eligibility for the study. Only after each individual had met strict criteria for eligibility was he included in the study.

Since the Air Force investigators had reviewed the complete military record of each member of the study cohorts, they were certain that the Comparisons had not handled or worked with dioxin-containing herbicides during their military careers. Prior to the start of the study, there was no method to determine whether the study participants had worked with herbicides in civilian life. However, an extensive series of questions concerning non-military employment and leisure activities was included in each of the physical examinations so that possible exposures to dioxin in non-military activities could be assessed. To date, only one of the Comparisons has reported having worked in a chemical plant that produced herbicides. This individual was also identified on the National Institute of Occupational Safety and Health (NIOSH) roster of dioxin-exposed industrial workers. One other individual was identified on the NIOSH roster, but he is not an active participant in the ongoing study. Our initial assumption that the Comparisons were not significantly exposed to dioxin has been strongly supported by the results of the serum dioxin pretest where only one of the Comparisons had a dioxin level (21 parts per trillion) that was above the normally accepted background level.
This individual has worked in a steel plant for the past five years handling waste chemicals.

Question 2: How will the serum dioxin assay affect study power?

Answer 2: Previous analyses of relative risk have been based on the assumption that the Ranch Hands, as a group, were exposed to dioxin and that the Comparisons have not been exposed. This assumption has not been questioned until recently. Although we suspected that some small proportion of the Ranch Hand cohort may have been only slightly exposed, we had no data with which to

OASD(PA) DFOISR 88-T-1939

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verify our suspicion. Now that the dioxin assay and more accurate estimates of half-life are available, these assumptions can be validated. The results of the recently released dioxin study of 150 Ranch Hands and 50 Comparisons suggest that some Ranch Hands may not have been significantly exposed to dioxin during or subsequent to duty in Vietnam. This conclusion is still somewhat uncertain because without the availability of blood collected during the early post-Vietnam years, we can not determine whether those Ranch Hands who currently have low levels were never exposed or have had their body burden of dioxin decay to background levels in the interval since their duties in Vietnam. Forty percent of the Ranch Hands in the initial serum study had serum levels of dioxin below 20 parts per trillion (ppt) and 20 percent had levels below 10 ppt. Other studies of dioxin levels by the Centers for Disease Control (CDC) suggest that 20 ppt is the upper limit for U. S. residents without known dioxin exposure. Since the mean value for the 50 Comparisons included in the initial study was below 10 ppt, there is probably some degree of variation in background levels within the United States.

Estimates of the increase in statistical power arising from the use of the serum dioxin assay are dependent on the disease condition of interest, its prevalence in the absence of exposure to dioxin, the number of participants in the study and the proportion of Ranch Hands who were in fact never exposed to dioxin. Given the uncertainties regarding the actual background levels of dioxin in the United States, 70 percent of the Ranch Hands might be considered as having been significantly exposed. If there were a doubling of risk for a relatively common disease such as skin cancer, the power of the AFHS to detect it would increase from 90 percent to 100 percent. The power would increase from 85 percent to 100 percent in the more extreme case if only 60 percent of the Ranch Hands were actually exposed.

The fixed sample sizes in this study limit our ability to detect a doubled risk when the disease prevalence is 1 percent or less. However, the corrective effect of using the serum dioxin assay is nevertheless substantial. If 70 percent of the Ranch Hands were truly exposed, the power of the study to detect a doubling of risk for a disease with a 1 percent prevalence increases from 20 percent to 42 percent. Further, the use of the assay will enhance the power to detect a tripling of risk from 52 percent to 85 percent for such rare diseases and conditions.

Question 3: Further thoughts on the skin cancer findings.

Answer 3: The finding of an increased incidence of skin cancer in the Ranch Hand group is of concern to the Air Force. The investigators have taken geographic residence into account in their analysis of this finding and plan to investigate it more thoroughly in the analysis of the data collected during the 1987 physical examination. No further conclusions can be made at this time.

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Question 4: What was the range of serum dioxin levels in enlisted fliers?

Answer 4: Of the 150 Ranch Hands who participated in the initial serum dioxin study, 19 were enlisted fliers and 131 were enlisted ground personnel. The mean dioxin levels in the fliers was 22.7 ppt; the mean in the ground personnel was 53.3 ppt. The three highest values in the fliers were 36, 40 and 127 ppt, and the highest in the ground personnel were 211, 303 and 313 ppt. The lowest value in the fliers was 3.6 ppt and the lowest in the ground personnel was 3.2 ppt. These data certainly suggest that the enlisted fliers were exposed, but not to as great a degree as were the ground personnel. This observation suggests that the apparent increase in systemic cancer among the enlisted fliers is not related to dioxin exposure, since the flying group had lower exposures to dioxin.

Question 5: Did the serum levels vary with occupational group?

Answer 5: The only two Ranch Hand occupational groups represented in the initial serum study were enlisted fliers and enlisted ground personnel. These two groups did differ in their current levels of dioxin. The initial study was intentionally restricted to these two groups because the Air Force investigators believed that they would contain the most heavily exposed men.

Question 6: Why were there no cases of chloracne found in the Ranch Hand group?

Answer 6: The presence of chloracne was evaluated by medical history, physical examination and by reviews of the military medical records of each participant. There was no evidence that chloracne had occurred in the Ranch Hand cohort. Despite what appear to be significantly higher exposure to dioxin containing chemicals among most members of the Ranch Hand cohort, the absence of chloracne (the "hallmark" of dioxin exposure following industrial accidents) is most likely due to levels of exposure that were below the threshold required to produce this condition.

Question 7: Was there over-reporting of birth defects in the AFHS?

Answer 7: The Air Force investigators have not yet completed the verification of the health status of the more than 6,000 children fathered by the study participants, and I can not comment on the presence or absence of differential reporting in the study. In view of the findings of the CDC study, errors in accurate reporting by parents are not unexpected in our data. In fact, we have observed errors where parents reported birth defect that were not verified by medical records and others where reportedly normal children did have verified defects. Definitive answers to these questions will not be available until after we have completed the verification process and analyzed the data.

Question 8: Were semen tests conducted on AFHS participants?

Answer 8: Semen studies were included in the initial physical examinations of the AFHS in 1982. Assessments of the total sperm count and the percentage of abnormally shaped sperm were made. At

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that time, all measurements were made with manual methods rather than the automated methods used in the CDC study. The results of the AFHS semen studies were published in the February 1984 report, and no significant differences were found between the Ranch Hand and Comparison groups, with 13 percent of the Ranch Hands and 12 percent of the Comparisons having abnormally low sperm counts (below 20 million per milliliter). Using the manual methods, 4.8 percent of the Ranch Hands and 4.7 percent of the Comparisons had excessive numbers of sperm with abnormal morphology (shape).

Question 9: Explain the statement "a subtle but consistent decrease in group differences between the 1984 and 1987 studies".

Answer 9: This statement refers to the observation that the number of statistically significant differences and the degree of difference between the two groups decreased by the time of the 1987 report. This trend is reflected by the drop in the relative risk for skin cancer from 2.5 in the 1984 report to 1.6 in the 1987 report and the absence of group differences in depression, hypochondria, Babinski reflexes and peripheral pulses. These findings do indicate that the two groups are becoming more homogeneous with the passage of time.

Question 10: Is the serum dioxin test valid and reliable?

Answer 10: I feel that the serum dioxin test as performed by the scientists at the CDC is indeed a valid and reliable measure of significant exposure to dioxin, even if that exposure occurred 20 or more years ago. The assay is as accurate and reliable as any research medical laboratory assays. The quality control procedures in place at the CDC are exceptionally stringent and repeated measurements of the same sample produce results that have a coefficient of variation of only 15 percent. The coefficient of variation is a measure of variation due to laboratory error, and this level of variation indicates that an individual having a reported dioxin level of 10 ppt can be confidently regarded as having a true level between 5.5 and 14.5 ppt. A level of 15 percent for an assay of this complexity reflects the highest standards of laboratory quality.

The estimate that the half-life of dioxin is seven years is accurate. That estimate is based on the analysis of blood collected by the AFHS in 1982 and again in 1987. A value of seven years is obtained even when two different mathematical methods are used to calculate the half-life. The estimate of seven years has a confidence interval of between six and nine years. This variation is entirely explained by the variation of 15 percent in the assay itself, and therefore the estimate is as accurate as possible.

The availability of this assay will alleviate the necessity to make assumptions about the level of individual exposure to dioxin in Vietnam and assumptions about the lack of exposure in civilian occupations and leisure activities. It will permit the Air Force investigators to develop a single exposure index for all of the study participants rather than the three independent indices now in use. This will enhance the statistical power of the data

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analysis and additionally eliminate a potentially major source of misclassification.

The serum assay will put the assessments of exposure on nearly the same footing as the assessments of disease. Thus, within the limits of laboratory variability, we will know as much about the current levels of dioxin as we know about liver, endocrine and kidney function. This situation is unprecedented in epidemiologic studies of dioxin's effects. More specifically, the strongest possible evidence for or against a dioxin effect on health may now become apparent. Should we find a pattern of statistically significant increases in disease with increased dioxin levels, we will have clearly implicated dioxin as a cause of ill health. Conversely, should we find no relationship between disease and dioxin levels, we will have strong evidence exonerating dioxin.

Question 11: How will the scope of the second follow-up report differ from the first follow-up report?

Answer 11: The second follow-up examination, conducted in 1987, was similar to that of the first two examinations (the Baseline in 1982 and the first follow-up in 1985). However, the examination format was refined for the most recent examination. The quality control of the skin testing was significantly enhanced, immunological testing was upgraded to reflect the state-of-the-art in 1987, the psychological assessment was improved and some modifications were made to the panel of clinical laboratory tests used in the study. The analysis of these and improved sources of data will be included in the next report. If we are able to complete the serum dioxin assays as quickly as we would like, the assay results could be used in some of the exposure index analyses.

Question 12: Describe the scientific review process.

Answer 12: The Air Force investigators work closely with the contractor's staff to conduct the data analyses, interpret the data and prepare the study report. The report is sent directly to the Advisory Committee for the AFHS, which is appointed by the Agent Orange Working Group. The committee meets with the Air Force and contractor scientists to discuss the report. After the report has been accepted by the committee, it is sent to the Air Force Surgeon General for public release. At no point in the process is there any pressure from Air Force management to alter the report or modify its conclusions.

The report authored by Dr. Richard Albanese (USAFSAM TR 88-3) did not follow this procedure. It was reviewed by the Advisory Committee in an early draft and was not approved. It was subsequently released following an alternative procedure generally used for other scientific and technical reports generated by Air Force scientists.

The Air Force investigators are currently preparing a report summarizing the 1987 report for submission to a scientific peer-reviewed journal. Unfortunately, the task of reducing the extensive study reports to an acceptable size yet retaining sufficient detail to make them scientifically meaningful is extremely difficult. In the past, there has been insufficient time between other study requirements to accomplish this job. Hopefully, the investigators will be able to complete this task later this year.

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QUESTIONS FOR MGEN SLOAN, AF/SG

1. Air Force comments on the verification of self-reported birth defects:

In Dr. Wolfe's 25 August 1987 letter to Senator Daschle he states: "Verification of all reported birth defects in the children fathered by the participants in our study was conducted using medical records and birth certificates in 1984. Sixty-one percent of the defects reported by the Ranch Handers and their wives and 63% of those reported by the comparisons were verified as codable defects." At that time, none of the "normal" children's records had been reviewed. The current team of Air Force investigators and the Advisory Committee felt that the analysis was premature and unsuitable for valid interpretation without full verification of all births.

The preliminary analyses of birth defects did not account for clustering of birth defects within families and grouped the reported defects by body organ system rather than by whether or not they could have been caused by direct toxic effects on the developing fetus or by altered or mutated chromosomes of the parents (biological mechanisms).

The investigators felt that it was imperative to review records from all children fathered by study participants. This process of record retrieval and review for more than 6,000 children is expected to be completed in November 1989, with a published report anticipated during the summer of 1989.

Within the past year, Air Force statisticians have developed new statistical approaches to these data and have obtained new statistical techniques from the Centers for Disease Control (CDC) that will accommodate family genetic history. They have also worked with CDC geneticists and epidemiologists to devise analyses that will account for biological mechanisms. There has never been any attempt to mislead, delay or cloud the resolution of the birth defect issue.

2. The Air Force's "1988 interim report on the Ranch Hand Study."

It is correct that this 1988 report and the 1984 report did reach essentially the same conclusions. From the 1984 report: "This baseline report concludes that there is insufficient evidence to support a cause-and-effect relationship between herbicide exposure and adverse health in the Ranch Hand group at this time. The study has disclosed numerous medical findings, mostly of a minor or undetermined nature, that require detailed follow-up." From the 1988 report: "In six of 11 clinical areas, statistically significant group differences occurred, and in five of these six instances, the group differences were in the direction of expected dioxin effects. Dioxin cannot be confidently identified as the causative agent of these findings at this time. ... However, dioxin is not exonerated as a causative agent. ..." Therefore, our study is a planned 20 year research effort.

Technical Report 88-3 contrasted the 1984 data with a literature search concerning dioxin. The clinical areas Dr. Albanese highlights were, in fact, clearly mentioned in the 1984 report as exhibiting group differences. These areas, in turn, were

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subjected to more intensive follow-up evaluation during subsequent phases of the ongoing study.

The observation of an increase in systemic cancer among the subgroup of enlisted fliers in the Ranch Hand group is of great interest, but its relevance is unknown at this time. The finding is based on only five cases of cancer in the Ranch Hand enlisted fliers. The occurrence of only two cases in the comparisons would make the finding no longer statistically significant. It is interesting to note that in an equivalent group of men from the general population, one would expect to find two cases. This may indicate that the finding could represent a decrease in the comparisons rather than an increase in the Ranch Hands. We anticipate that the ground enlisted personnel were generally more exposed to dioxin than were the enlisted fliers, and that group did not exhibit any differences in cancer.

The Air Force team of investigators is fully committed to pursue these observations in subsequent mortality and morbidity reports, using improved measures of exposure derived from the serum dioxin assay.

3. The Air Force scientists' confirmation in their testimony of four conclusions relating to the Air Force Health Study that Senator Daschle sets forth:

Birth Defects

The investigators agree that the increase in reported birth defects in the children of Ranch Hand personnel is an important finding, but the relevance of this observation must await the results of the reanalysis using fully verified data. The effect of differential patterns of reporting, both over-reporting and under-reporting can have drastic impact on the results of the analysis. In the Vietnam Experience Study, the CDC found that Vietnam veterans reported a statistically significant number of birth defects as compared to the control group. However, when these reports were verified the difference was no longer statistically signficant.

The Exposure Index

The investigators agree that the exposure index used in the 1984 and 1987 analyses was subject to limitations. It is an exposure estimate based upon the best calculation of the effective number of gallons of herbicide to which the airmen were exposed. It was based on an estimate of gallons of herbicide sprayed each month (1962-1971), the levels of dioxin contamination and the number of men assigned each month. Individual exposure estimates could not be made. While this method was limited it was state-of-the-art at the time. These limitations were clearly discussed in each of the published reports, and concern for these limitations led to an intensive program to use the serum dioxin determination as an improved measure of exposure.

The testing of an initial group of 200 study participants did indeed confirm that some of the Ranch Hands were heavily exposed to dioxin. The mean level of dioxin in the serum of the 147 Ranch Hand participants was 10 times higher than that of the 49

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comparisons.

The 1988 Interim Report

The USAFSAM Technical Report 88-3, authored by Dr. Richard Albanese and released in February 1988, is technically correct. Both Colonel Wolfe and Dr. Michalek did work with Dr. Albanese in the preparation of the report. However, they were unable to reconcile differences with Dr. Albanese concerning the tone and writing style of the report and withdrew their names as co-authors.

4. The exposure index used in the Ranch Hand Study:

Our initial work developed an estimated exposure index that reflected the best calculation of the number of gallons of herbicide to which the Ranch Hand members were exposed. It was based on the estimate of the number of gallons of herbicide sprayed per month (1962-1971), the levels of dioxin contamination and the number of men assigned each month. Individual exposure measures could not be made. Calculations of indices of this type is a standard approach in epidemiologic studies of occupational groups. The index was based on assumptions of individual work habits since industrial hygiene data were not collected or maintained on the Ranch Hand operation. A separate index was constructed for each occupational category. It was recognized that this index was not precise, but it was the state-of-the-art in epidemiologic methods. The limitations of the index, the assumptions implicit in its construction and the preliminary nature of the results were clearly stated by the authors in the previous Air Force reports.

5. The use of blood analyses to determine dioxin levels in the Ranch Hand Study participants:

The ability to improve the estimated exposure index with the serum dioxin test is a major opportunity in the scientific evaluation of the Agent Orange issue. This new serum dioxin assay will provide a precise measure of the current body burden of dioxin for each of the 2,010 men who contributed blood for this portion of the study. From this data, the investigators will be able to combine all of the study participants into a single-exposure analysis rather than the three occupation specific analyses currently used.

Another outcome of the serum analysis method is the estimation of the half-life of dioxin in humans. Initial calculations indicate that the half-life is approximately seven years.

6. Government interference in dioxin studies, especially in the peer review procedures, and the effects thereof:

Senator Daschle continues to express concern that there has been undue government and management interference with the conduct of the Air Force Health Study. Colonel Wolfe, Dr. Michalek and Dr. Albanese were clear in their letter to Senator Daschle in August 1987, as well as in their discussion with him in January 1988 and in their testimony on 12 May that there has not been any interference in their work. They have been free of interference throughout the study, and all decisions have been made on the basis of scientific merit. The Advisory Committee of the Agent Orange Working Group provides review and oversight functions. Their advice and counsel has been extremely valuable to the study. Once they have approved a document or report, it is released by the Air Force Surgeon General in that form. At no time has there been technical direction of the study from non-scientific elements. The Air Force, through the Surgeon General's office, limits its management to administrative matters of funding, manpower and equipment. A statement was made in the Protocol of the Air Force Health Study (written in 1978 and 1979) that a committee should be established to provide scientific review of the study and guidance to the Air Force investigators. The suggested makeup of that committee included a "veteran's representative." The Protocol statements were written prior to the establishment of the Science Panel of the Agent Orange Working Group (AOWG) and were intended by the authors as a guide to the creation of an external review group. This suggestion was superseded by the creation of the Advisory Committee by the AOWG. The Air Force position is that membership on the Advisory Committee should be based primarily on scientific accomplishment and expertise. The Advisory Committee has periodically recommended modifications to preliminary versions of the study documents and reports. Changes made were made to address scientific issues raised during the review process.

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Questions for Dr. Joel Michalek, Principal Investigator

Question 1: This February, the Air Force released "United States Air Force Personnel and Exposure to Herbicide Orange" which reviewed the morbidity of Ranch Hand personnel in eleven clinical areas. In written testimony submitted to the Committee, the Air Force contended that the "conclusions [of the 1988 report] were essentially the same as in previous reports' The Air Force has also described the 1984 Ranch Hand study as "reassuring." Is it fair to say the birth defects information included in the 1988 report is new to the public?

Answer 1: Yes, the reported birth defect information in the 1988 report is new to the public. As I have already testified, it corrects the baseline analysis of reported birth defects by showing that the group difference seen at baseline is not restricted to minor defects of the skin, but is, in fact, independent of severity. The word "reassuring" was used in the baseline report to indicate that the Ranch Hands were not experiencing the adverse health conditions claimed as resulting from exposure to Agent Orange by veteran activists in the media. The new reported birth defect analysis of baseline data does not alter the conclusions of the baseline report or in particular, make the results less reassuring to the Ranch Hands because, as the recent CDC study shows, reported birth defect data can be biased. The baseline reported birth defect finding has motivated a medical record verification of the birth defect status of every child fathered by the Ranch Hands and their matched Comparisons. A final report of the verified birth defect analysis will be ready by August 1989.

Question 2: Do you think the 1988 report communicates more effectively than the 1984 report that dioxin has not been exonerated as a cause of health damage?

Answer 2: It is implicit in the 1984 report that dioxin has not been exonerated. The 1988 report makes the statement explicitly. In fact, dioxin can never be "exonerated" by epidemiologic studies. At best, up to limitations in statistical power and exposure estimation, epidemiological studies can only address the question as to whether occupational exposure to dioxin is harmful. Such studies cannot establish whether occupational exposure to dioxin is safe. Hence, the statement that dioxin has not been exonerated is, in logical terms, a tautology.

Question 3: Mr. Don Newman, Chairman of the Agent Orange Working Group, testified that "we are seeing no cause-effect relationship between service in Vietnam and possible exposure to Agent Orange and adverse health." To evaluate the existence of a cause and effect relationship between a chemical and the incidence of disease, one might be expected to look for a dose-response relationship. Such an analysis requires some measure of "dose" or, in this case, extent of exposure to Agent Orange. Isn't it true, however, that the Ranch Hand study does not, in its current form, have an accurate Agent Orange exposure estimate?

Answer 3: The current exposure estimate for a Ranch Hand is simply the amount of dioxin sprayed divided by the number of men available of the same rank and job as the subject Ranch Hand during

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his tour.

This estimate was the best that could be devised and has had wide precedent in the field of epidemiology. For example, similar exposure estimates were applied in epidemiologic studies of occupational exposure to asbestos. Since the recent application of the CDC's serum dioxin assay to 150 Ranch Hand enlisted personnel, we have discovered, for the first time, that the exposure index is uncorrelated with current dioxin body burden. This information is new and, as yet unpublished. It certainly suggests that the current exposure index is not as accurate as we had once thought.

Question 4: In your testimony before the Committee, you noted that "the absence of a good exposure measure attenuates our ability to discover dioxin's effects." Could you explain your comment more fully?

Answer 4: While the estimated exposure index was the best measure available at the time our study began, plots of the exposure index versus current dioxin body burden suggest that the exposure index has overestimated the dioxin exposure of some Ranch Hands and underestimated the dioxin exposure of other Ranch Hands. Assumptions inherent in that index could have limited its ability to detect a true association between exposure and disease. Thus, unless the true association is very strong, we may be unable to detect it with the original exposure index. In other words, as I have testified, the absence of a good index attenuates (diminishes) our ability to discover an effect of dioxin exposure.

Question 5: Much of the recent discussion of Agent Orange levels concerns the use of blood serum tests. In your estimation, what is the most reliable measure of exposure to dioxin? Would a reliable measure be based solely on blood tests, or would you include other factors, as well? In addition, please compare and evaluate the exposure measures used in the aborted CDC study of Agent Orange, the New Jersey Agent Orange Commission study, and the Air Force Ranch Hand study.

Answer 5: The blood test results offer the first opportunity to apply current dioxin body burden measurements to assess Ranch Hand exposure to dioxin. We do not currently know how best to use this information to assess exposure. There are at least two issues that must be resolved before the CDC assay can be applied to assess individual exposure; they are: (1) Is route of entry (cutaneous, ingestion, inhalation) an important determinant of serum lipid dioxin body burden? and (2) Does dioxin half-life vary significantly with age, percent body fat, metabolic rate or disease state? To address the first of these, we have begun an extensive in-house review of dioxin pharmacokinetics. The second issue is the motive for in-house development of a regression analysis of half-life. We expect to have answers to these questions within one year. If route of entry is an important determinant, assessments of exposure might be adjusted for military occupation (flying, ground), since it is currently believed that flyers received more exposure via inhalation than through the skin. If currently measurable attributes, such as weight changes, are found to

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influence half-life, exposure analyses will be further adjusted for weight changes since Vietnam. Thus, the future exposure assessment may not be based solely on the blood tests. The specifics of that exposure assessment will depend on current work in pharmacokinetics and the statistical theory of half-life estimation.

The CDC, in its aborted ground troop study, and the Air Force in its Ranch Hand study applied demographic and work history data to assess dioxin exposure. These methods have wide precedent in the field of epidemiology, having been successfully used in studies of asbestos, radiation and toxic chemical exposures. These indices were considered the best available methods for measuring dioxin exposure until the CDC began applying the serum dioxin assay to epidemiologic cohorts in 1987.

In the aborted CDC study, investigators assessed exposure in several ways, all based on data regarding troop locations and dates, Ranch Hand spray paths and dates, toxicological data regarding the decay of dioxin in sunlight and personal estimates of exposure. A "hits" model was developed in which a "hit" was defined as any occasion on which a veterans company had a recorded location within two kilometers of an area that had been sprayed with Agent Orange in the previous six days. For each veteran; a hits score was compiled by summing all of his "hits" during his tour in Vietnam.

The Air Force index was based on monthly records of gallons of herbicide sprayed and personnel records that permitted job categorization of all Ranch Hands. The index for a given Ranch Hand was simply the amount of dioxin sprayed divided by the number of men in his job category during his tour.

Both metrics depend on the "Herbs Tape" data for gallons sprayed per month. Both metrics are subject to error and it is reasonable to expect that the CDC metric would be less accurate than the Air Force metric, since troop locations were only approximately known. The Air Force metric could be inaccurate because gallons sprayed per month were not identified by base in the Herbs Tape data and this could have little relationship to the exposure of a particular Ranch Hand or even groups of Ranch Hands.

No exposure index is identified in published accounts of the New Jersey Agent Orange Commission study. Questionnaire information on approximately 2700 veterans was reviewed to identify 100 men who "seemed likely to have handled herbicides during a tour duty in Vietnam". Thus, New Jersey investigators were studying self-reports of herbicide handling and, I assume, tour dates and data of the kind available on the Herbs Tape to determine whether the tour occurred during a period of heavy spraying. Since the New Jersey Commission has not published a formulation of their exposure index, I have no opinion about its accuracy relative to the Air Force and CDC indices.

Question 6: The Vietnam Experience Study, conducted by the Centers for Disease Control, includes a "Reproductive Outcomes and Child Health" report. In it, the CDC notes a statistically significant difference in reported birth defects between Vietnam

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functional stimulation variables. The results are summarized in Table 1.

Table 1
Statistical contrasts of
Ranch Hands versus Comparisons on Immunological Variables

Cell surface markers	Unadjusted	Adjusted
Total T cells (T11)	NS	****
Helper T cells (T4)	NS	NS
Suppressor T cells (T8)	NS	NS
B cells	NS	****
Monocytes	NS	****
HLA-DR cells	NS	****
T4/T8 ratio	NS	NS
Functional Stimulation		
Unstimulated response (PHA)	NS	NS
PHA net response	NS	NS
Pokeweed net response	NS	NS
MLC net response	NS	****

In Table 1, NS indicates a non significant group mean difference and **** indicates the presence of a statistically significant group by covariate interaction. A group by covariate interaction occurs when the Ranch Hand versus Comparison mean difference changes with the values of a covariate. The interactions indicated in the table are summarized in Table 2.

Table 2
Immunology Interaction Summary

Variable	Interaction
Total T cells	Group by race
B cells	Group by smoking history among non-Blacks
Monocytes	Group by occupation Group by current alcohol consumption
	Group by current alcohol consumption
MLC net response	Group by pack-year

Overall, no discernible pattern was identified in these interactions to suggest a detriment in any subgroup of either Ranch Hands or Comparisons.

Additionally, exposure index analyses of cell surface markers revealed no pattern consistent with a dose response relationship. For enlisted ground crew, the mean total T cell and suppressor T cell counts for the medium exposure level were

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and non-Vietnam veterans. The differences were based on telephone interviews with the two groups of veterans. To verify the differences, the CDC conducted a substudy of a smaller group of veterans who were scheduled for medical examinations. The smaller group was not selected randomly, included less than one-sixth of those in the original study, and relied on hospital birth records only. Could you comment on the adequacy of the procedure the CDC used to verify reported birth defects in the Vietnam Experience Study?

Answer 6: It is true that the 2282 veterans selected for the hospital birth record substudy were not randomly selected from the 15,288 veterans interviewed; they were, in fact those who participated in both the interview and the physical and who were examined after January 1, 1986. Detailed analyses of the examined veterans relative to the telephone interview participants did not show different demographic characteristics or health histories. In addition, participation in the substudy was high in both the Vietnam and non-Vietnam cohorts, and, moreover, the two cohorts were similar with respect to various demographic and military covariates. Thus there was no evidence of selection bias or participation bias in the substudy. Regarding the use of hospital birth records, as opposed to all medical records up to the age of 18, the purpose of the CDC birth defect verification was only to validate the reported birth defect rates derived from the questionnaire. The CDC investigators believed, as I do, that hospital birth records would suffice for that purpose. Additionally, hospital birth records are less subject to verification bias, a phenomenon wherein Vietnam veterans may be more sensitive than non-Vietnam veterans to the birth defect status of their children and so be more inclined to have them seen at medical facilities where defects would be discovered and reported. Thus, even if Vietnam and non-Vietnam Veterans had identical birth defect rates in their offspring, Vietnam veterans 'children would appear to have more verifiable defects than children of non-Vietnam veterans if this bias were operating. This is a potential bias that we will face in the currently evolving Ranch Hand birth defect verification, which considers hospital birth records and medical records up to the age of 18. Finally, I believe that CDC restricted their verification to hospital birth records because a wider search, of the kind we are doing, would have taken years to complete. In summary, I believe the CDC's use of hospital birth defect records was appropriate for their purpose and that the non-random selection of fathers for the verification substudy did not bias their results.

Question 7: During her testimony to the Committee, Hellen Gelband of the Office of Technology Assessment commented that there were no immune differences between the Ranch Hand population and the control group in the Ranch Hand findings. Is this true? Please include an explanation of the adjusted analyses in your answer.

Answer 7: Unadjusted and adjusted Ranch Hand versus Comparison contrasts were performed on seven cell surface markers and four

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significantly lower than those of the low exposure level, but were slightly lower than those of the high exposure level. The exposure index analysis of the functional stimulation tests revealed no consistent significant doseresponse patterns for net PHA counts or net MLC counts. For net pokeweed counts, enlisted flyers in the high exposure level had a significantly lower adjusted count than enlisted flyers in the low exposure level, and a decreasing trend with exposure was apparent.

In summary, Air Force investigators concluded that no significant group differences were present for the cell surface marker or functional stimulation studies and that there was no indication of impaired immunologic competence in either group. Hellen Gelband therefore agrees with the Air Force interpretation of these data.

Question 8: Major Jack Spey of the Ranch Hand Vietnam Association asserted that the Ranch Hand ground crew were more heavily exposed than the enlisted flyers. I know some ground crew members were tested in your blood tests, and I know the Air Force plans to test all Ranch Hand study participants, but I am unaware of tests already done on the enlisted flyers. Have the serum dioxin levels of the enlisted flyers or the pilots been tested? If so, please describe your findings.

Answer 8: Of the 150 Ranch Hand enlisted personnel who participated in the 1987 pilot dioxin study, recently reported in the MMWR, 19 were flying enlisted and 131 were enlisted ground personnel. The mean dioxin body burden among the flying enlisted was 22.7 ppt (parts per trillion) and the mean dioxin body burden for enlisted ground crew is 53.3 ppt. This breakout by occupation, flying versus ground, was not presented in the MMWR paper; it is currently under investigation. These data suggest that Major Jack Spey was correct in his assumption that enlisted ground personnel were more heavily exposed than enlisted flying personnel.

Question 9: Dr Barnes from the VA's Advisory Committee on Environmental Hazards testified that biological factors affect the movement and storage of dioxin in the body. Is this true? If so, could you explain how this fact affects half-life estimates and the reliability of an exposure measure based on blood tests?

Answer 9: It is true that, in theory, biological factors, such as weight changes and disease states, affect the movement and storage of dioxin in the body. We will take these factors into account with adjusted half-life estimates before applying the dioxin assay results to exposure estimation in the Ranch Hand cohort. The development of the statistical theory of adjusted half-life estimation is currently under way at the USAF School of Aerospace Medicine.

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QUESTIONS FOR RICHARD A. ALBANESE, MD

Question 1: In your answer to a question at the hearing concerning your motivation for writing the 1988 report, you responded that you wanted to make clear that the Ranch Hand results were inconclusive; Agent Orange could not be exonerated, nor could it be proved to be a cause of disease. Your scientific objectivity may confuse some observers. I'd like to ask you a question, and request a yes or no answer. Is it fair to say that dioxin may be actively causing ill health among Ranch Handers?

Answer 1: Yes, in my opinion, it is fair to say that dioxin may be actively causing ill health among Ranch Handers.

Question 2: The Ranch Hand Advisory Committee/Peer Review Group recommended changes to the conclusions of the original 1984 Ranch Hand report, which had the effect of deemphasizing the evidence linking dioxin exposure to health disorders in the Ranch Hand population. The same Advisory Group recommended withholding the December 1984 report on birth defects in the Ranch Hand population. In addition, the Advisory Group recommended revisions of the February 1988 report. In your view, why has the Advisory Group taken these actions?

Answer 2: I do not fully concur with the three recommendations of the Ranch Hand Advisory Committee that you have mentioned. I do not understand the Advisory groups recommendations in terms of scientific data and methodology. I believe the Advisory Committee recommendations were influenced by its composition which is not in accord with the specifications of the study protocol. Particularly, the protocol requires that the Advisory Committee contain scientific members nominated by veterans advocacy groups. To my knowledge, such members were not present on the Advisory Committee, and, in my opinion, their absence has had the effect that an important point of view has been incompletely represented.

In an epidemiological study, through the choice of critical levels in statistical testing and other aspects of data interpretation, the researcher influences the risk or probability that the taxpayer will be incorrectly or unjustly required to pay for an injury not caused by government action, and the researcher influences the risk or probability that society will fail to care for an individual who has been hurt by a government action. Different researchers weigh these two risks differently because of individual, personal values.

It is because of the subjective, value-laden aspects of public health work that it is recommended that advisory groups be composed so that all interests are represented. The need to have all constituencies represented seems clearly articulated by Dr. Kotin in his 1979 Sappington Memorial Lecture published in the Journal of Occupational Medicine. Further, the research of Professor Nicholas Steneck at the University of Michigan, Collegiate Institute for Values and Science, demonstrates through detailed case studies, the intimate interaction of science and values in public health issues, and the great importance of balanced representation on standard setting panels (references: N.H. Steneck. The Microwave Debate. The M.I.T. Press 1984; N.H. Steneck. "Subjectivity in Standards:

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The Case of ANSI C95.1-1982." Microwaves & RF, May 1983, page 137.)

The Ranch Hand study protocol, understanding the importance of constituency representation, required scientific personnel nominated by veterans advocacy groups to be members of the Advisory Group. To my knowledge, this representation has not occurred.

Question 3: The Ranch Hand study protocol, which was written carefully to protect the integrity of the study, requires that the Advisory Group contain "approximately equal representation...between government scientists, academic scientists, and scientific personnel nominated by veterans advocacy groups." To your knowledge, did the Advisory Group meet this protocol requirement? If not, please explain.

Answer 3: To my knowledge, the Advisory Group did not meet the protocol requirement that the group contain scientific personnel nominated by veterans advocacy groups. I cannot explain this departure.

Question 4: Are you aware of other departures from the Ranch Hand study protocol?

Answer 4: In my opinion, Air Force scientists have been fastidious and expert in their adherence to the protocol. I believe that a peer review group augmented by an appropriate number of scientists nominated by veterans groups would improve interpretation of data in the Ranch Hand and other governmental studies.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Centers for Disease Control
Atlanta GA 30333

JUL 25 1988

The Honorable G. V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This is in response to your June 24 letter with follow-up questions from the Subcommittee on Hospitals and Health Care hearing of June 8, 1988. Enclosed are our responses to your questions.

Thank you for your interest in this important issue.

Sincerely yours,

James O. Mason

James O. Mason, M.D., Dr.P.H.
Assistant Surgeon General
Director

Enclosure

Questions Submitted to Dr. James O. Mason from the Subcommittee on Hospitals and Health Care June 8, 1988, Hearing.

1. QUESTION:

In your statement, you refer to studies being conducted by the National Institute for Occupational Safety and Health. Are there any preliminary results that you can tell us about?

ANSWER:

NIOSH is conducting two epidemiologic studies:

1. A retrospective cohort mortality study of about 7,000 workers from 14 U.S. chemical plants, who were assigned to the production of substances contaminated with 2,3,7,8-TCDD. This study is comparing the rates and causes of death in the workers with those in the U.S. population.

2. A cross-sectional medical study of about 400 workers from 2 of the 14 plants and an unexposed comparison group matched to the workers by age, sex, race, and neighborhood. This study examines medical outcomes, such as neurologic and immunologic deficiencies, which have been hypothesized to be associated with the exposure of dioxin. The study also includes interviews of the spouses of the participants to ascertain reproductive outcomes such as fetal loss and fertility. This study does not have adequate power to evaluate birth defects.

Both studies are in the early stages of analysis. There are no preliminary results regarding the effects of exposure on mortality or health outcomes.

Two related small studies have been completed. Both report on analyses of levels of 2,3,7,8-TCDD in the workers and in a comparison group, and both studies demonstrate clearly that the production workers have the highest human levels of 2,3,7,8-TCDD ever reported.

The first study, "Levels of Polychlorinated Dibenzo-p-dioxins (PCDDs) and Dibenzofurans (PCDFs) in Workers Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin" was presented in October 1987 at the Seventh International Conference on Dioxin in Las Vegas, Nevada. The study is now being submitted for publication. The study showed that nine production workers who made products contaminated with 2,3,7,8-TCDD at a Missouri chemical plant had a mean adipose tissue level (lipid adjusted) of 355 parts per trillion (ppt); 7 workers from the same plant who were never assigned to contaminated production processes had a mean of 14.7 ppt (background levels in humans have been found to be under 20 ppt).

The second study, "Levels of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in the Serum of U.S. Chemical Workers Exposed to Dioxin Contaminated Projects: Interim Results," will be presented at the Eighth International Conference on Dioxin in Umea, Sweden, on August 21, 1988. This is an evaluation of all of the completed laboratory analyses of 2,3,7,8-TCDD in serum samples from the workers in the NIOSH cross sectional medical study described above. To date, 46 analyses have been completed. The mean serum level of 2,3,7,8-TCDD in 27 workers formerly employed at a New Jersey chemical plant in production of substances contaminated with 2,3,7,8-TCDD is 194 ppt (lipid adjusted); the mean in 19 unexposed referents is 8.0 ppt. These results confirm the findings of the earlier study of Missouri workers. It is of interest that the worker with the highest level (717 ppt) would have had a level of over 14,000 ppt when he terminated employment at the plant in 1956, based upon the assumption that there is a 7 year half-life for loss of 2,3,7,8-TCDD in humans (CDC, MMWR 37:309-11, 1988). A recent study of levels of 2,3,7,8-TCDD in German production workers (Beck, et al., Levels of PCDD's in Adipose Tissue of Occupationally Exposed Workers, in press) found similar high levels in production workers who made products contaminated with 2,3,7,8-TCDD.

2. QUESTION:

As you know, the VA's Proportionate Mortality Study found increased deaths in Marine Vietnam veterans from lung cancer and non-hodgkins lymphoma. Will you say something about your findings in the Vietnam Experience Study on these two conditions?

Are there other studies which shed light on lung cancer and its association with dioxin?

ANSWER:

In evaluating the results of the Vietnam Experience Study, it is important to realize that the numbers of specific types of cancer are too few to draw firm conclusions. For non-Hodgkin's lymphoma, seven confirmed cases were identified in the Vietnam group compared to one confirmed case in the non-Vietnam group. One confirmed lung cancer case was identified in the Vietnam group compared to two confirmed cases in the non-Vietnam group. We have provided additional information on the interpretation of the non-Hodgkin's lymphoma data in our May 20 and June 23 letters to you and Congressman Solomon and Senators Cranston and Murkowski (copies attached).

We have enclosed a list (Attachment I) of several studies which examined the association between lung cancer (as well as other health outcomes) and Vietnam service or exposure to herbicides. Most of these were mortality studies and were not specifically designed to examine only lung cancer. The continued follow up of the Ranch Hand cohort and the results of the National Institute for Occupational Safety and Health (NIOSH) Production Workers Study might help clarify this issue.

3. QUESTION:

In the Vietnam Experience Study, statistically significant differences were found with respect to four areas: past hepatitis B infection; low sperm concentration; stool occult blood; and high frequency hearing loss. Will you comment on the significance of each of those findings?

ANSWER:

The increased hearing loss in Vietnam veterans, particularly among those who had tactical military occupational specialties, is consistent with the results of several studies of military which show that exposure to military noise results in irreversible hearing impairment. Similarly, the higher prevalence of past hepatitis B infection among Vietnam veterans may be related to service in a country where this viral infection is endemic. The small increase in stool occult blood is unexplained. This finding was rare, however, affecting 1.3% of the Vietnam and 0.5% of the non-Vietnam veterans in this study. The sperm findings are also unexplained. We evaluated several factors that are known or suspected to affect sperm characteristics (e.g., age, race, current use of alcohol, drugs, certain medications, etc.) and none of these accounted for the differences in sperm characteristics. We also did not find that the more prevalent psychological disturbances experienced by Vietnam veterans, including anxiety, depression, and post-traumatic stress disorder, accounted for these differences.

While low sperm concentrations, low levels of morphologically normal sperm, and low percentages of motile sperm have traditionally been used as indicators of reduced fertility potential, the average number of children fathered per veteran (for those who had semen samples analyzed) after their primary tour of duty was similar, 1.4 for Vietnam veterans and 1.5 for non-Vietnam veterans. The average number of children fathered per veteran for the entire Vietnam and non-Vietnam cohorts was identical, 1.6. Also, the rates of birth defects (for those who had semen samples analyzed) as determined by birth record information were similar, 5.9% for Vietnam and 5.7% for non-Vietnam veterans' children.

4. QUESTION:

What are the consequences of a low semen count or a reduced proportion of morphologically normal sperm cells? Specifically, has either an increase in birth defects or inability to conceive been associated with either of these conditions?

ANSWER:

The answer to this question is basically provided in the answer to Question #3. An additional point is that we are not aware of any studies among humans that have clearly shown that poor semen quality is related to adverse reproductive outcomes or birth defects.

5. QUESTION:

What relevance does the Vietnam Experience Study have for the issue of health effects of exposure to Agent Orange?

ANSWER:

The Vietnam Experience Study was not designed to evaluate the issue of possible health effects of exposure to Agent Orange.

6. QUESTION:

Will the blood test for the presence of dioxin that you have validated solve the problem of exposure that stopped the Agent Orange study?

What contribution would be made to the issue of possible health effects of Agent Orange by blood testing Ranch Handers?

ANSWER:

The blood serum test for dioxin (2,3,7,8-TCDD) is certainly a better method of exposure assessment for Army ground troops than the use of incomplete military records. However, the results of CDC's TCDD Validation Study found that the median dioxin levels in a group of 646 Vietnam veterans (Army ground troops) were identical to a group of 97 non-Vietnam veterans (Army ground troops)--3.8 parts per trillion (ppt). Additionally, background levels of TCDD in the general population with no known exposure can range up to 15-20 ppt, and only 2 of the 646 Vietnam veterans had levels greater than 20 ppt. These findings suggest that those ground troops who were not involved in the direct spraying or handling of herbicides in Vietnam were not highly exposed to Agent Orange. On the basis of these findings, the Agent Orange Working Group and the Congressional Office of Technology Assessment recommended cancellation of the Agent Orange Study. The use of serum dioxin testing would make an essential contribution to the issue of possible health effects of Agent Orange in Ranch Handers.

7. QUESTION:

Please expand on the category of immunosuppressant disabilities in terms of what one might learn from the Vietnam Experience Study.

ANSWER:

We tested all of the men who participated in the medical examination (2,490 Vietnam veterans and 1,072 non-Vietnam veterans) for cell-mediated immunodeficiency and laboratory assays of T and B lymphocytes and found no evidence of any differences between the Vietnam and non-Vietnam groups in these immune system measurements.

8. QUESTION:

We understand that there are only two laboratories in the world that can perform the blood assay test for the presence of dioxin in human blood. What are the problems in other labs becoming equipped to perform the test?

ANSWER:

Serum dioxin levels are very difficult to measure because of their very low concentration and the complicated interferences of other compounds. An exacting high-resolution gas chromotography/mass spectroscopic method using advanced state-of-the-art instrumentation is required to measure serum dioxin at these low levels. In addition, a labor-intensive sample preparation requiring about 19 hours of separation column cleanup per sample is needed to remove interfering compounds.

Another laboratory performing serum dioxin measurements would need to (1) obtain the methodology from CDC, (2) purchase and adequately operate an advanced high-resolution gas chromatography/mass spectrometer (cost: approximately $400,000), and (3) establish a laboratory section devoted to the extensive sample preparation procedure.

9. QUESTION:

In the blood validation study part of the Agent Orange study, only two veterans had dioxin levels in their blood that exceeded background levels. How do you explain these two levels? How likely is it that this is representative of the larger population of Vietnam veterans?

How do you reconcile the overall lack of exposure found in that study with reports of veterans that they did receive substantial exposure?

ANSWER:

We have no specific explanation for the two individuals with dioxin levels greater than 20 ppt. The veteran with a level of 45 ppt reported no exposure (military or civilian) to herbicides; the veteran with a level of 25 ppt reported 180 days of indirect military exposure (defined as walking through, or clearing vegetation in, a previously sprayed area), plus one day of home use, but no other exposure. Both men reported their health as "excellent," with no health problems perceived as a consequence of exposure to Agent Orange.

We chose the sample of Army Vietnam veteran ground troops for the TCDD Validation Study primarily from battalions that had the greatest "opportunity for exposure" based on information contained in the military records. Although we do not know if this sample is representative of the larger population of Army Vietnam veteran ground troops, it is important to note that, in evaluating the potential for herbicide exposure, this group of 646 Vietnam veterans served an average of 320 days in tactical battalions which operated in the heaviest sprayed area of Vietnam (III Corps) during the peak years of Agent Orange spraying (1966-69).

Regarding reconciling the lack of exposure found in the Validation Study (compared to veterans' reports of substantial exposure), the "type" of exposure may offer an explanation. The results of the Validation Study, together with the findings to date of dioxin levels in Ranch Handers, suggest that veterans who were not involved in direct spraying or handling of herbicides in Vietnam (as opposed to walking through areas or clearing vegetation that had been sprayed) were not heavily exposed to Agent Orange. On the other hand, many of those who were directly involved in the spraying or handling of herbicides do have elevated dioxin levels today.

10. QUESTION:

The Kansas City study of agricultural workers found an increase of non-hodgkins lymphoma in those exposed to a herbicide. What do you believe is the relevance of the Kansas City study with respect to veterans' exposure to Agent Orange in Vietnam?

What is the significance of the differences in the nature of the exposures in the Kansas City Study and in Vietnam?

ANSWER:

In answering this question, we want to clarify that the study referred to was conducted in the State of Kansas, not Kansas City. This study found a strong association between frequent agricultural use of 2,4-dichlorophenoxyacetic acid (2,4-D) and the risk of non-Hodgkin's lymphoma (Hoar, et al., 1986). Although Agent Orange was a formulation of 50 percent 2,4-D and 50 percent 2,4,5-trichlorophenoxyacetic acid, there are factors that make generalization of these results to Vietnam veterans' risk of non-Hodgkins lymphoma difficult. First, the two scenarios, agricultural herbicide use as studied by Hoar et al. and Vietnam herbicide exposure, differ widely with respect to many parameters that influence cancer risk. Among these are formulation, frequency and duration of exposure, methods of application, and other possible hazardous exposures and conditions. Second, while the results from CDC's Agent Orange Validation study suggested that few Vietnam veterans were heavily exposed to Agent Orange, the Kansas study reported the highest risk in farmers with the greatest yearly 2,4-D exposure. Thus, given the suspected rarity of Agent Orange exposure among Vietnam veterans, the attribution of any cancer increase to Agent Orange will be difficult.

11. QUESTION:

Dr. Gochfeld of the New Jersey Agent Orange study has suggested in his testimony that in terms of education, the Centers for Disease Control Vietnam veteran group was very much different from the non-Vietnam veteran comparison group: 14 percent of Vietnam veterans had not completed high school compared with 11.6 of non-Vietnam veterans; and, 17.8 percent of Vietnam veterans were college graduates while 21.7 percent of non-Vietnam veterans were college graduates. Please comment on these differences.

ANSWER:

The purpose of the Vietnam Experience Study was to evaluate the health effects that may have resulted from the "general experience" of having served in Vietnam. We attempted to identify two groups of men that were, at the time of enlistment, as similar as possible with regard to military factors (other than Vietnam service) that might be associated with health status. At the time of the telephone interview, 14.1% of the Vietnam and 11.6% of the non-Vietnam veterans had less than high school education, whereas the corresponding percentages of veterans who were college graduates were 17.8% and 21.7%, respectively. Whether these percentages are "very much different" is a matter for interpretation. It does appear, however, that these differences are not related to one group's having served in Vietnam, but rather are related to preexisting (i.e., before entry into the Army) differences in the two study groups. The average General Technical (GT) test score (a measure of general aptitude) taken at the time of enlistment was about 3 points lower for the Vietnam group than for the non-Vietnam group. After using statistical techniques to account for these differences in test scores (and the five other preexisting or "entry" characteristics not related to Vietnam service), we found that the percentage of Vietnam and non-Vietnam veterans who graduated from college was not statistically different. Thus, after accounting for preexisting factors not related to military service, we found that Vietnam and non-Vietnam veterans have attained similar levels of education.

Another concern might be that these differences in educational attainment could affect our analyses of other health outcomes related to Vietnam service. That is, these educational differences could obscure the "real" association between Vietnam service and a particular health outcome. This is unlikely, since in all analyses we have accounted for the potential influence of education upon health outcomes. We have done this two ways--indirectly, by adjusting the results for differences in enlistment GT test scores (and the five other entry characteristics not related to Vietnam service), and directly, for certain outcomes, by including educational level in the statistical analyses. These differences, between Vietnam and non-Vietnam veterans, in educational attainment do not appear to have affected our comparison of the two groups. For nearly all health conditions, the unadjusted estimates were similar to the estimates that were adjusted for the six entry characteristics as well as to estimates that were adjusted for education.

12. QUESTION:

Please identify the geographic areas in Vietnam where veterans with confirmed cases of non-hodgkins lymphoma served.

ANSWER:

Four of the seven Vietnam veterans with non-Hodgkin's lymphoma served in the III Corps region and one served in the II Corps region. The other two served in two different areas--one in I Corps and III Corps, and one in II Corps and III Corps.

ATTACHMENT I

Other studies examining lung cancer risk. (This list is not all inclusive.)

1. Lawrence CE, Reilly AA, Quickenton P, et al. Mortality patterns of New York State Vietnam veterans. American Journal Public Health 75:277-79, 1985.

2. Lynge E. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. British Journal of Cancer 52:259-70, 1985.

3. Riihimaki V, Asp S, Hernberg S. Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland. Scandanavian Journal of Work & Environmental Health 8:37-42, 1982.

4. Zack JA, Suskind RR. The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident. Journal of Occupational Medicine 22:11-14, 1980.

5. Anderson HA, Hanrahan LP, Jensen M, et al. Wisconsin Vietnam veterans mortality study. Wisconsin Div. of Health, Madison, WI, 1986.

6. Holmes AP. West Virginia Vietnam-era veterans mortality study. West Virginia Health Dept., Charleston, WV, 1986.

MAY 20 1988

The Honorable G.V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

The purpose of this letter is to provide updated information from the Vietnam Experience Study about certain cancers which has become available since our testimony for the Senate hearings was prepared. An identical letter is being sent to Congressman Gerald B. Solomon. We have also communicated this information to the Senate Committee on Veterans' Affairs.

Since the testimony presented at the Senate hearings on May 12, 1988, we have completed the review of medical records in an effort to validate the cases of non-Hodgkin's lymphoma and lung cancer reported by Vietnam and non-Vietnam veterans in the Vietnam Experience Study telephone interview. Prior to the testimony, all of the records were not available. Based on the results of this validation, combined with the data from the mortality component of the Vietnam Experience Study, we have identified seven confirmed cases of non-Hodgkin's lymphoma in the Vietnam group compared to one confirmed case in the non-Vietnam group. As for lung cancer, we have identified one confirmed case in the Vietnam group compared to two confirmed cases in the non-Vietnam group. These numbers differ slightly from those reported during the hearing and represent the current and final data from the Vietnam Experience Study. Additional cases of these cancers may be identified in the future if additional mortality updates of these cohorts are done.

The data contained in the above paragraph were not part of the Vietnam Experience Study as published in the Journal of the American Medical Association. The original protocol stated that the number of these cancers in the two cohorts would be so small that it was necessary to construct a special study for these cancers. Thus, the Selected Cancers Study is being conducted. With heightened concern about non-Hodgkin's lymphoma in the past 6 months, we decided to try to obtain the medical records on the veterans who reported anything that could possibly be associated with this disease. We thus obtained 50 records, and the 8 cases cited above were identified. At the time the testimony was prepared for the Senate, not all records necessary to validate the findings had been received; thus, we reported three unconfirmed and three confirmed cases in the Vietnam veteran population and one confirmed in the non-Vietnam veteran population. The remaining records for validation were received on May 17. While the difference between seven and one appears substantial, the data cannot be interpreted with certainty because we did not obtain all medical records on all the veterans interviewed. The final interpretation of the data on non-Hodgkin's lymphoma awaits completion of the Selected Cancers Study.

Page 2 - The Honorable G.V. (Sonny) Montgomery

With respect to the Selected Cancers Study, we plan to conduct a preliminary analysis of the data collected to date on non-Hodgkin's lymphoma and to submit this analysis to the Agent Orange Working Group Science Panel and the Office of Technology Assessment for peer review. Following these reviews, we could provide the findings to the House and Senate, noting the limitations of this preliminary analysis of the non-Hodgkin's lymphoma data. We anticipate that this process will take approximately 3 months. It should be noted that these data can only be considered preliminary, and the limitations may be so severe that it would not be wise to report them until the study is completed late in 1989 or early in 1990.

Sincerely yours,

James O. Mason

James O. Mason, M.D., Dr.P.H.
Assistant Surgeon General
Director

cc:
Administrator of Veterans Affairs

IDENTICAL LETTER TO CONGRESSMAN GERALD B. SOLOMON
AND SENATORS CRANSTON AND MURKOWSKI

JUN 2 3 1988

The Honorable Alan Cranston
Chairman, Committee on Veterans' Affairs
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

Because of the continued interest in the non-Hodgkin's lymphoma (NHL) data contained in our May 20 letter to you, we are providing additional information on the interpretation of these findings. An identical letter is being sent to Senator Frank Murkowski as Ranking Minority Member of the Senate Committee on Veterans' Affairs.

The finding from the Vietnam Experience Study (VES) of seven cases of NHL in the Vietnam group versus one case in the non-Vietnam group should be interpreted cautiously. Although the difference between these numbers is statistically significant ($p=0.04$), other points need to be considered before biologic significance is assumed. First, the result could still be due to chance given the enormous number of comparisons made in the VES. Second, the NHL cases are not homogeneous in regard to cell-type. For example, two of the Vietnam veterans had Burkitt's lymphoma, a type of lymphoma which is exceedingly rare in the United States and is thought to have a different origin from other non-Hodgkin's lymphomas. Third, the time of diagnosis should be considered. One of the Vietnam veteran cases was diagnosed with NHL while serving in Vietnam, while two of the other Vietnam veterans were diagnosed within 3 and 4 years of leaving Vietnam. Since environmentally related cancers usually exhibit a longer latent period than observed in these veterans, it is doubtful whether these "early cases" are related to military service. A fourth point to consider is the "expected number" of NHL cases in the two groups. Based on average annual age-specific U.S. incidence rates reported by the National Cancer Institute (SEER, 1973-1977), 3.9 cases of non-Hodgkin's lymphoma would be expected in Vietnam veterans and 3.5 cases would be expected among the non-Vietnam veterans. While these results show more cases than expected in the Vietnam group and less than expected in the non-Vietnam group, this comparison should be interpreted cautiously given the methodologic differences between SEER and the VES.

Finally, in judging the relevance of our finding, we examined results of other studies of Vietnam veterans and found these results to be inconsistent with respect to NHL. Most of the studies, though small, are negative. Only two prior reports indicate excess mortality from NHL—the Wisconsin State study and the Veterans Administration (VA) study. Furthermore, the VA results indicate an excess of NHL in Marines, but not in Army veterans. In fact, the VA findings show a deficit in NHL mortality among Army Vietnam veterans. It is difficult to reconcile our finding with the one based on Army personnel in the VA study. If there was a strong risk factor for NHL in Vietnam, we would expect to see a consistent indication of it in most, if not all, studies.

We hope this additional information is helpful in clarifying these findings.

Sincerely yours,

James O. Mason

James O. Mason, M.D., Dr.P.H.
Assistant Surgeon General
Director

cc:
Administrator of Veterans Affairs
Chief Medical Director, Veterans Administration

Identical letters to be sent to:

The Honorable Frank Murkowski
Ranking Minority Member
Committee on Veterans' Affairs
United States Senate
Washington, D.C. 20510

The Honorable C.V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20510

The Honorable Gerald B. Solomon
Ranking Minority Member
Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20510

June 22, 1988

NOTE TO DR. MASON

The attached letter is at the request of Jonathan Steinberg, Chief Counsel, Senate Veterans' Affairs Committee. He would like to have this if possible by close of business on Thursday since the Committee is apparently is going to vote on Murkowski's bill to compensate non-Hodgkin's lymphoma.

For your information, I have enclosed a copy of Mr. Murkowski's press release that was passed out at the House hearings. Despite the cautions we put in our letter on interpretation of these data, he did not take them.

Vernon N. Houk, M.D.
Assistant Surgeon General
Director
Center for Environmental Health
and Injury Control

Attachments

NEWS

U.S. SENATOR
FRANK
MURKOWSKI
OF ALASKA

FOR IMMEDIATE RELEASE　　June 7, 1988
CONTACT: Richard Paul　　(202) 224-3924

MURKOWSKI ASKS V.A. TO LINK CERTAIN CANCER AND VIETNAM SERVICE

Washington, D.C. -- Citing findings which suggest a seven-times higher rate of a particular type of cancer among Vietnam veterans, the Ranking Republican Member of the Senate Veterans' Affairs Committee, Senator Frank H. Murkowski, has requested that the Veterans' Administration (VA) take action that would declare the cancer to be connected to Vietnam service and provide disability compensation to Vietnam veterans suffering from the disease.

The Centers for Disease Control recently examined cases of non-Hodgkins lymphoma (NHL), which many claim can be linked to the use of the defoliant Agent Orange. They found that veterans who served in Vietnam and whose health was evaluated in conjunction with their Vietnam Experience Study, developed seven cases of the disease. Those veterans who did not serve in Vietnam developed only one case.

More complete findings on this subject will be available in 1989 or 1990, but Murkowski called the CDC's current numbers "significant in their own right" and said they "constitute a reasonable basis for immediate action."

-MORE-

The action recommended by the Alaska Senator would be a "presumption of service-connection," under which VA would assume that NHL was associated with service in Vietnam. Such a finding would enable Vietnam veterans with the disease and their survivors to receive disability compensation and other benefits.

In a letter to VA Administrator Thomas Turnage, Murkowski pointed out that there is a precedent which would allow VA to administratively find service-connection for NHL. "VA has administratively determined that the deaths due to heart disease of veterans service-connected for double above-the-knee amputations should be service-connected based on finding that such amputees suffer a disproportionate amount of heart disease."

Murkowski urged Turnage to "take the initiative in response to CDC's findings," pointing out that quick action could, among other things, "do much to disarm critics of the VA who allege the agency is unwilling to assist Vietnam veterans unless compelled to do so." Murkowski also said action would "diffuse pressure" on Congress to pass laws that would issue broad presumptions of service-connection.

-MORE-

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta GA 30333

JUL 18 1988

The Honorable G. V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This is in response to your letter of July 5 forwarding additional questions resulting from the June 8, 1988, hearing before the Subcommittee on Hospitals and Health Care. Our responses are enclosed. In order not to be repetitive, we have reversed the order of the two questions.

Sincerely yours,

James O. Mason

James O. Mason, M.D., Dr.P.H.
Assistant Surgeon General
Director

Enclosure

1. Question:

Why does the Vietnam Experience Study report in the Journal of the American Medical Association omit any specific mention of the non-Hodgkin's lymphomas?

Answer:

The data on non-Hodgkin's lymphoma were not part of the Vietnam Experience Study as published in the Journal of the American Medical Association. The original protocol stated that the number of these cancers in the two cohorts would be so small that it was necessary to construct a special study for these cancers. Thus, the Selected Cancers Study is being conducted. With heightened concern about non-Hodgkin's lymphoma in the past 6 months, we decided to try to obtain the medical records on the veterans who reported anything that could possibly be associated with this disease. We, thus, obtained 50 records and confirmed 7 cases in the Vietnam veterans group and 1 in the non-Vietnam veterans group. At the time the testimony was prepared, not all records necessary to validate the findings had been received; therefore, we reported three unconfirmed and three confirmed cases in the Vietnam veteran population and one confirmed in the non-Vietnam veteran population. The remaining records for validation were received on May 17. While the difference between seven and one appears substantial, the data cannot be interpreted with certainty because we did not obtain all medical records on all the veterans interviewed. The Selected Cancers Study, when completed, will provide more definitive information on the risk of non-Hodgkin's lymphoma among Vietnam veterans.

2. Question:

The Vietnam Experience Study found that seven of the Vietnam veterans had non-Hodgkin's lymphoma, and only one veteran who had not served in Vietnam had non-Hodgkin's lymphoma. I understand that all of those cases have been confirmed. Several previous studies have also suggested a possible causal link between dioxin and non-Hodgkin's lymphoma. How do you interpret these findings?

Answer:

We know of no studies suggesting a causal link between dioxin and non-Hodgkin's lymphoma. The most creditable study is the National Cancer Institute's study of agricultural workers in Kansas that suggests an association with the use of the herbicide 2,4-D and non-Hodgkin's lymphoma. The dioxin of concern from service in Vietnam is 2,3,7,8-TCDD. The 2,4-D is not contaminated with that dioxin. In addition, the TCDD Validation Study showed, based on serum dioxin measurements, that Army ground troops were unlikely to have been exposed to dioxin in Vietnam.

In addition, the finding from the Vietnam Experience Study of seven cases of non-Hodgkin's lymphoma in the Vietnam group versus one case in the non-Vietnam group should be interpreted cautiously. Although the difference between these numbers is statistically significant ($p=0.04$), other points need to be considered before biologic significance is assumed. First, the result could still be due to chance given the enormous number of comparisons made in the Vietnam Experience Study. Second, the non-Hodgkin's lymphoma cases are not homogeneous in regard to cell-type. For example, two of the Vietnam veterans had Burkitt's lymphoma, a type of lymphoma which is exceedingly rare in the United States and is thought to have a different origin from other non-Hodgkin's lymphomas. Third, the time of diagnosis should be considered. One of the Vietnam veteran cases was diagnosed with non-Hodgkin's lymphoma while serving in

Vietnam, while two of the other Vietnam veterans were diagnosed within 3 and 4 years of leaving Vietnam. Since environmentally related cancers usually exhibit a longer latent period than observed in these veterans, it is doubtful whether these "early cases" are related to military service. A fourth point to consider is the "expected number" of non-Hodgkin's lymphoma cases in the two groups. Based on average annual age-specific U.S. incidence rates reported by the National Cancer Institute (SEER, 1973-1977), 3.9 cases of non-Hodgkin's lymphoma would be expected in Vietnam veterans and 3.5 cases would be expected among the non-Vietnam veterans. While these results show more cases than expected in the Vietnam group and less than expected in the non-Vietnam group, this comparison should be interpreted cautiously given the methodologic differences between SEER and the Vietnam Experience Study.

Finally, in judging the relevance of this finding, we examined results of other studies of Vietnam veterans and found these results to be inconsistent with respect to non-Hodgkin's lymphoma. Most of the studies, though small, are negative. Only two prior reports indicate excess mortality from non-Hodgkin's lymphoma--the Wisconsin State Study and the Veterans Administration (VA) study. Furthermore, the VA results indicate an excess of non-Hodgkin's lymphoma in Marines, but not in Army veterans. In fact, the VA findings show a deficit in non-Hodgkin's lymphoma mortality among Army Vietnam veterans. Our finding is difficult to reconcile with the one based on Army personnel in the VA study. If there were a strong risk factor for non-Hodgkin's lymphoma in Vietnam, we would expect to see a consistent indication of it in most, if not all, studies.

THE UNDER SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JUL 29 19[illegible]

The Honorable G. V. (Sonny) Montgomery
Chairman
Committee on Veterans'Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

Thank you for your letter of July 5, 1988 which has several follow up questions to my testimony before your Subcommittee on Hospitals and Health Care hearing of June 8, 1988.

As the questions for the most part pertain to the mandate of the Domestic Policy Council Agent Orange Working Group (DPC/AOWG), I have given a historical background since the inception of the group.

Additionally, I have included my testimony and that of Dr. James Mason, Director, Centers for Disease Control who accompanied me before the Senate Committee on Veterans Affairs on May 12, 1988.

Should you have any further questions please do not hesitate to call on me.

Sincerely,

Don M. Newman
Under Secretary

Follow-up Questions for June 1988, Hearing on Agent Orange Legislation and Oversight Issues from Congressman Sonny Montgomery, Chairman, to the Agent Orange Working Group

Background

In order to respond some historical information is essential in answering these questions specifically and precisely. The Domestic Policy Council Agent Orange Working Group established by President Reagan had its genesis in the Interagency Work Group (IWG) to study the possible long-term effects of phenoxy herbicides and contaminants. The IWG had been chartered by the White House on December 11, 1979. 1/ Its mission was to monitor, coordinate and set priorities among Federal Government research activities, to design a research agenda, to organize the means to assure that the research agenda is carried out, and to assure that all research findings, whether publicly or privately financed, be promptly made available to the public and to the Congress.

In response to the concerns of veterans' groups that exposure to herbicides in Vietnam could be presenting health problems, President Reagan on July 17, 1981 expanded the membership of the IWG; renamed it the Agent Orange Working Group (AOWG) and raised its status to Cabinet Council Working Group level. 2/ The IWG's mandate was reaffirmed with stated emphasis on research relating to Agent Orange exposure. 3/

In addition, the AOWG was charged with guiding the Congressional mandated epidemiological study of Vietnam Veterans exposed to Agent Orange. 4/ The Congress in authorizing this study directed the President to assure that the study be fully coordinated with other on-going or future studies. 5/

The legislative history relative to this presidential responsibility states: "The Committees also stress the importance of the provision directing the President to assure (preferably through an interagency task force) that the mandated study be fully coordinated with on-going or future governmental studies...." 6/

The Act was later amended to authorize an expansion of the scope of the epidemiological study to include an evaluation of the adverse health effects which may have occurred as a result of other factors that may have been present in Vietnam. 7/ The

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1. Memorandum for Secretary of Defense, Secretary of Health, Education and Welfare, Administrator of Veterans Affairs from Stuart Eizenstat, Assistant to the President for Domestic Affairs and Policy, Subject: Interagency Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants, December 11, 1979.
2. Memorandum for Secretary Richard Schweiker, Chairman Pro-Tem, Cabinet Council on Human Resources from Robert Carlson, Executive Secretary of Human Resources Cabinet Council, Subject: Agent Orange Working Group, July 17, 1981.
3. Memorandum for Secretary of Defense, et al from Secretary Richard Schweiker, Chairman Pro-Tem, Cabinet Council on Human Resources, Subject: Agent Orange Working Group, August 21, 1981.
4. Veterans Health Programs Extension and Improvement Act of 1979, Sec. 307(a), 93 Stat. 1097, P.L. 96-151.
5. Ibid., Sec. 307(c), 38 U.S.C. 219 note.
6. 125 Congressional Record 34992, December 6, 1979.
7. Veterans' Health Care, Training, and Small Business Loan Act of 1981, Sec. 401, 95 Stat. 1061, P.L. 97-62, 38 U.S.C. 219 note.

amendment did not disturb the direction given to the President regarding coordination of the study nor was the delegation of this presidential responsibility to the AOWG affected. Consequently, the AOWG is charged, in this one instance only, to oversee and coordinate the Vietnam Experience component of the congressionally authorized study even though the study component is not concerned with the health effects of exposure to Agent Orange.

Q1. Isn't it true that you recently sent a memo to members of the Agent Orange Working Group requiring that all reports and press releases regarding Agent Orange be reviewed by and cleared through the Agent Orange Working Group before being released to the public?

A. Yes, I sent such a memo on April 1, 1988 (copy enclosed) as a reminder to the DPC/AOWG members and Science Panel members.

Q2. In that memo, you state that the "Agent Orange Working Group was given the responsibility for reporting to the public the results and implications of all research in the Agent Orange area." Can you share with us the specific language in your mandate which gives you this responsibility? [If this information isn't availability, could it be provided for the record after the hearing?]

A. The White House charter for the Agent Orange Working Group (AOWG) states in pertinent part that the AOWG shall: "Assure that all relevant research findings, whether publicly or privately financed, are promptly made available to the public and the Congress, in a comprehensible and comprehensive fashion."

Q3. This memo is dated April 1, 1988. What prompted you to circulate the memo in April of this year? [NOTE: The memo is dated ten days after public release of the report by Dr. Richard Albanese, "United States Air Force Personnel and Exposure to Herbicide Orange," which concluded that Agent Orange could not be exonerated as a cause of disease among Air Force Ranch Handers who handled and sprayed Agent Orange in Vietnam.]

A. It was no coincidence that the April 1, 1988 memorandum was sent. From time to time there has been a need to remind members of the Agent Orange Working Group of the Domestic Policy Working Group (DPC/AOWG) of their responsibility to ensure that all scientific studies are carefully peer reviewed by the Science Panel of the Agent Orange Working Group and released to the public in a comprehensive and comprehensible fashion.

Sensational or self-serving reports or reviews of previously reported data, serve only to disillusion the veteran seeking the answers. We owe our nation's veterans the best scientific analysis available in the search for answers. In addition, it is important that all AOWG members and the White House be aware of releases in order to be prepared for follow-up questions which might arise.

Q4. Your memo states that "the release of any report, without the review mandated by the Agent Orange Working Group procedures, could constitute a serious breach and may undercut our credibility." What does this mean? Presumably all government Agent Orange studies are peer reviewed by independent scientists before being released. Why would the release of a valid report undercut the credibility of the Agent Orange

Working Group? Wouldn't that be possible only if the report questioned the prevailing view within the Agent Orange Working Group that a causal link between Agent Orange and disease has not been sufficiently established to justify compensation to Vietnam veterans?

A. The release of any report by any agency of the Executive Branch without review by the AOWG would be a serious breach of the duty imposed on the Executive by the Congress when it legislated that "the President shall assure that ...all appropriate coordination and consultation is accomplished between and among ...the heads of such departments, agencies, and instrumentalities that may be engaged, during the conduct of studies carried out pursuant to subsection (a), in the design, conduct, monitoring, or evaluation of such dioxin-exposure studies." This duty was imposed upon the President "(f) or the purpose of assuring that any study carried out by the Federal Government with respect to the adverse health effects in humans of exposure to dioxins is scientifically valid and is conducted with efficiency and objectivity."

This responsibility has been delegated to the AOWG. Although all studies are peer reviewed, the Congressional mandate provides for coordination and final evaluation to be accomplished by the President, in this case, the AOWG. Therefore, the release of any report without following AOWG procedures constitutes a serious breach of the duty owed to the President and to the Congress with regard to the efficient and objective manner in which agencies are approaching such studies. If the AOWG is circumvented or ignored, its credibility with the public and with the Congress is seriously jeopardized.

The AOWG is only concerned with assuring, as directed by the Congress, that all studies done by government agencies be reviewed and coordinated to the end that the study "is scientifically valid and is conducted with efficiency and objectivity."

Q5. In what sense would the release of a report without AOWG clearance constitute a "serious breach"? A serious breach of what?

A. The release of a Federal Government report without AOWG clearance is a serious breach of the duty delegated to it by the President who is responsible to the Congress by direct statutory mandate to assure validity, efficiency and objectivity.

Q6. Has Agent Orange been exonerated as a causative agent in human illness? Do we need more research on the relationship between Agent Orange and disease?

A. We are only saying that to date we are seeing no cause-effect relationship. The biggest obstacle is the Agent Orange exposure assessment. However, this obstacle is being hurdled in both the Ranch Hand and NIOSH Production Worker Study where TCDD serum analysis is being utilized as the exposure assessment. These two studies will directly address this issue of the cause-effect relationship. However, the just completed Vietnam Experience Study would appear to show that ground troops have no major health problems other than those related to stress. In response to your question concerning more studies, we don't need to design additional studies at this time; but we do need to await the results of the ongoing studies mentioned above as well as CDC's Selected Cancers Study which should be completed in early 1990.

Q7. Several studies of the effects of Agent Orange have attempted to develop measures of exposure. How accurate are those exposure measures? [The witness should say that the measures are not perfect] (SIC). Given the lack of precise measures of exposure, isn't it very difficult to draw conclusions about cause and effect between Agent Orange and disease?

A. The question of exposure was the prime cause that the Centers for Disease Control (CDC), after many attempts to develop an accurate exposure model, determined that a dependable epidemiological Agent Orange Exposure study could not be done. This is well explained in CDC Director Dr. James Mason's testimony before the Senate Veterans Committee on May 12, 1988 (copy enclosed).

The dose or extent of exposure are also well addressed in our testimony of May 12, 1988 before the Senate Committee. As Dr. Mason, who testified with me stated, "specific problems or lack thereof associated with Agent Orange experience, need to await the findings of the Air Force Health Study, and the National Institute of Occupational Safety and Health (NIOSH) Production Worker Study. In both these studies, exposure will be determined by serum values of TCDD measured by CDC".

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Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, DC 20510-8025

July 20, 1988

The Honorable G.V. (Sonny) Montgomery
Chairman
Committee on Veterans' Affairs
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

Enclosed are replies to the questions you sent me following the June 9, 1988 hearing of the Subcomittee on Hospitals and Health Care, concerning the health of Vietnam veterans. Responses to the questions accompanying your letters of June 24 and of July 5 are included.

Thank you for inviting me to present OTA's views on these issues, and for the opportunity to provide the additional information you requested.

Sincerely,

Hellen Gelband

Hellen Gelband
Senior Analyst

enclosure

RESPONSES TO QUESTIONS FROM THE SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE FOR HELLEN GELBAND, SENIOR ANALYST, OFFICE OF TECHNOLOGY ASSESSMENT JUNE 8, 1988 HEARING RECORD

1. The NCI Kansas Study found a two-fold increase in the risk of non-Hodgkins lymphoma associated with herbicide use, the western Washington study found no overall association with non-Hodgkins lymphoma and the VA's Proportionate Mortality study found increased deaths from non-Hodgkins lymphoma in Marines who served in Vietnam compared to Marines who did not serve in Vietnam. What is the significance of these different findings?

The individuals in the Kansas and western Washington studies who were judged "exposed" were known to have had direct occupational contact with herbicides and the various other chemicals included in the analyses. The Kansas study had the more precise information about exposures (including verification of chemical sales to a sample of farmers in the study); and the exposed cases and controls were generally a more homogeneous group in terms of exposure. They were all or nearly all farmers, whereas in the western Washington study, a variety of occupations were represented, and the variety of chemicals was greater. It is possible that the particular exposures that might have been responsible for the excess in Kansas were too infrequent, and information too imprecise for a fairly small relative risk, about two-fold, to be detected. It is also possible that the effect in the farmers was due to some combination of exposures. No specific information about exposure to Agent Orange was available for the VA Proportionate Mortality study. It is highly unlikely that many Marines had "occupational" exposure to herbicides. Their exposure profile is much more likely to resemble that of the Army ground troops. If a small proportion of them did have occupational exposures, it is almost inconceivable that the effect would filter through in a broad study such as the VA did. Particularly if an excess of deaths from lymphoma persists, it is important to search for risk factors or direct exposures that were commonly shared by the Marines but not by the Army.

2. What relevance do you see in the Kansas Study with respect to veterans' exposure to Agent Orange in Vietnam? How does the Kansas Study exposure relate to the Ranch Hand Study?

Exposures in the Kansas study were more like those of Ranch Handers and other herbicide applicators in Vietnam than of ground troops. It is likely that many of the "unexposed" in the Kansas study had environmental exposures--living on and around farms, using lawn chemicals--similar to many of the ground troops in Vietnam. The main difference between exposures in Kansas and the Ranch Hands is the distribution of exposure over time. The Kansas farmers generally used herbicides for many years, but only for fixed periods each year. The Ranch Hands, however, may have been in contact with Agent Orange every day or nearly so for their entire tour in Vietnam. Their exposures may actually have been somewhere between the farmers' exposures and exposure experienced by production workers, who handle chemicals every day.

3. In your opinion, is the test recently developed to measure dioxin levels in human blood a reliable and valid test for establishing exposure to Agent Orange?

Based on the information available so far, I'd say yes. If a person has a dioxin blood level significantly higher than background, that person must have been exposed to relatively high levels of dioxin at some time, since the test is quite specific, and dioxins are not synthesized by the body. The preliminary results of Ranch Hand analyses confirm that exposure to Agent Orange in Vietnam, with no significant subsequent exposure, is still readily detectable. The Ranch Hand dioxin group profile is entirely distinct from what was seen in ground troops. Currently, however, not enough is known about individual variation in the way dioxin is handled in the body to assert that someone with only background levels might not have had heavy exposure.

4. When the Air Force completes the dioxin tests on blood samples of Ranch Handers and links the results with the Ranch Hander health information, will there be any need to conduct other Agent Orange studies for veterans? That is, would a study of chemical corps workers in Vietnam using the dioxin blood test be expected to add to knowledge provided through the Ranch Hand Study using the dioxin blood test?

Using the dioxin blood test will sharpen up the Ranch Hand study considerably. Power lost through previous misclassification according to exposure group should be regained. Studying the chemical corps workers, if a larger number of them could be identified, could increase knowledge of possible dioxin effects, to the extent that they handled phenoxyherbicides. A problem with studying chemical corpsmen, however, is that, from what I understand, they handled many different chemicals, and it could be very difficult to isolate an Agent Orange effect, if that were the point of the study. If the point would be to identify potential adverse health effects of being a chemical corpsman, then they would be worth studying, if a large enough group could be identified.

5. What can you say about the selection of ground troops for inclusion in the CDC validation study of the blood test? How does this compare to the selection of troops for the New Jersey Agent Orange study printed in the Journal of the American Medical Association?

CDC chose Army ground troops who, according to the military records, served in the most heavily sprayed areas of III Corps during the periods of heavy spraying, but who were not herbicide applicators. The 10 veterans in the New Jersey "validation study" were chosen from among volunteer subjects, as those most likely to have had heavy exposure to Agent Orange. All but one were herbicide handlers. The one infantryman who was not a herbicide handler, but thought to have been heavily exposed environmentally, had only background dioxin levels.

6. The New Jersey Agent Orange Commission has been quoted as criticizing the exposure methodology used by the CDC in attempting the Agent Orange study. What is your opinion with regard to that criticism?

As I understand it, the criticism is directed mainly at the "hits model," which is an exposure ranking procedure based on the assumption that the men near areas shortly after the spraying (mainly Ranch Hand spraying) the largest number of times were those most likely to have had the greatest exposure. The approach conforms to the way exposure was commonly portrayed by veterans at the time the study was mandated: of men becoming contaminated by walking through sprayed areas, or being sprayed directly by Ranch Hand planes. The records of troop movements and herbicide spraying suggest that this was not a common scenario. It was recognized by CDC, as well as others, that some attempt had to be made to take into account non-Ranch Hand spraying (mainly Army helicopter, truck-mounted, and backpack spraying around base perimeters) in an exposure index. Although the participants in CDC's validation study were chosen using the hits model, they were also reclassified according to a number of other techniques, including the "area model," which is based on the total amount of Agent Orange sprayed in an area. In general, perimeter spraying went on in the same areas as did Ranch Hand spraying, so if it were an important source of exposure, I would have expected at least some of the men in CDC's sample to have had evidence of significant past exposure, which was not the case. I have never seen a written description of the exposure scheme the New Jersey researchers are using to classify ground troops, but I have heard that it is based on an intensive interview about where the man was in Vietnam and what he experienced. Until some men are classified by New Jersey, and the method confirmed by blood dioxin levels, there is no way of knowing whether their scheme is valid. In summary, I think CDC pursued all the leads they and others thinking about the issue found reasonable, and I think that, if there were significant exposure of ground troops, their methods would have identified at least some of them.

7. What can you say about the VA's Proportionate Mortality study finding of increased deaths from lung cancer among Marines who served in Vietnam?

The VA mortality study, discussed above (see NHL) reported finding about a 50 percent excess in the proportion of lung cancers in Marine Vietnam veterans. This finding is based on 130 lung cancer deaths. The Army Vietnam veterans showed no excess. Cigarette smoking is the most obvious potential cause of the excess lung cancer deaths. It would be logical to examine this possibility before searching for less plausible connections.

8. What evidence is there regarding the relation of Agent Orange exposure and immunosuppressive health effects?

I know of no studies relating specific immunosuppressive health effects to exposure to phenoxyherbicides or dioxin in humans, although severe immune effects, such as thymic atrophy, occur in laboratory animals after heavy dioxin exposure. In part, the lack of evidence in human beings may be because no group of conditions, other than a few associated with severe immunosuppression, is easily identifiable. A number of studies have, however, examined various laboratory measures of immune function. Children living in the area around Seveso at the time of the dioxin release there in 1976 have shown no immunologic deficits. No differences in immunologic function between Ranch Hands and their comparisons have been noted after extensive testing. CDC's Vietnam Experience Study, which also employed an extensive battery of immunologic measurements, also found no differences between Vietnam and Vietnam-era veterans.

The one study to date that has reported finding an immunologic deficit is of the residents of a heavily dioxin-contaminated trailer park in Missouri. In that CDC study, many laboratory measurements were made, with no significant differences noted between the exposed and controls. However, in a test for general immunologic reactivity, more of the exposed than control individuals lacked a response to immune stimulants. This result is difficult to interpret, particularly since there had been some problems with interreader variability in scoring the tests. There were no differences in immune-related disease patterns between the two groups. I believe some followup is ongoing in that population, but no results are available yet.

ADDITIONAL QUESTION SUBMITTED

1. The OTA has played an important role in reviewing Agent Orange research thus far, particularly with respect to the adequacy of various approaches and methodologies for studying this problem. In your estimation, how long will it take before we have definitive scientific answers about the toxicity of Agent Orange, or of dioxin? How many years will pass before science will be able to answer this question?

In my view, we have learned a great deal already about exposure to Agent Orange in Vietnam, and there is a substantial and growing base of information about the possible health effects of dioxin. If dioxin had very large and severe effects on exposed populations, I think we would already know that from studies of populations heavily exposed occupationally and environmentally. The ongoing studies of occupational cohorts from the NIOSH dioxin registry, and, in the case of Agent Orange, the Ranch Hand study, will continue to refine our knowledge about the possible health effects of these chemicals. There is rarely a particular point at which an "answer" appears, however. The "answer" at any given time is simply the best interpretation of the information then available.

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